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# Total Synthesis of (±)-Dysibetaine CPa and Analogs

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*Dedicated to the memory of Professor Tetsuo Shiba*

**Keywords:** Total synthesis / Natural products / Amino acids / Neurological agents / Diastereoselectivity / Chemoselectivity

The syntheses of the marine sponge-derived γ-amino carboxylic acid dysibetaine CPa and five analogs in their racemic forms were successfully performed by taking advantage of an electron-withdrawing *N*-(4-nitrophenyl) group in the cyclopropanation reaction, the reductive ring opening of an imide, and the ethanolysis of an *N*-Boc-protected imide.

## Introduction

Ligands for ionotropic glutamate receptors (iGluRs) are of particular importance for studying biological functions of structurally diverse iGluRs in the central nervous system, and a number of glutamate analogs, such as kainic acid, domoic acid, acromelic acid, and kaitocephalin, have been identified in natural resources.[1] *Lendenfeldia chondrodes*, a Micronesian marine sponge, contains the structurally diverse amino acids shown in Figure 1, that is, dysiherbaine (DH),[2] neodysiherbaine (NDH),[3] dysibetaine (DB),[4] and dysibetaines CPa (DBCPa, **1**) and CPb (DBCPb, **2**).[5] DH and NDH are glutamate analogs with potent convulsant activity.[6] DH exhibits a high affinity toward iGluRs such as recombinant GluK1 and GluK2 kainate receptors (KARs),[7] whereas NDH binds to GluK1 and GluK2 with 15- to 25-fold lower affinities.[8] Previously, we demonstrated that the structural modification of natural products by de novo organic synthesis is a useful approach to efficiently develop ligands with new specificities for iGluR subunit proteins. That is, we synthetically developed MSVIII-19, which lacks functional groups at the C-8 and C-9 positions of the DH structure, as a weak partial agonist for KARs. MSVIII-19 binds with a high affinity, but exhibits extraordinarily low efficacy, thereby acting as a functional antagonist of GluK1 KARs, and i.c.v. (intracerebroventricular) injection (0.002–0.020 mg/mouse) results in a coma-like unconscious state for up to 6 h in vivo.[6,8–11]

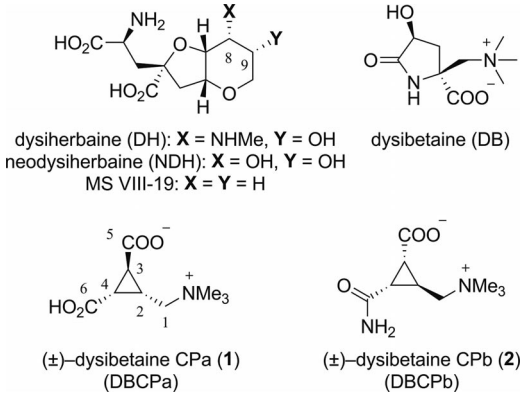


Figure 1. Amino acids isolated from *L. chondrodes* and synthetic analog MSVIII-19.

DBCPa (**1**) and DBCPb (**2**), whose isolation and structure were reported in 2004,[5] are cyclopropane carboxylic acids bearing quaternary ammonium groups. From a structural point of view, **1** and **2** have attracted significant attention as potential ligands for neuronal receptors such as γ-aminobutyric acid (GABA) receptors, as they incorporate a GABA motif. However, at most only a weak affinity to iGluRs has been clarified for **1** and **2** in radioligand binding assays, that is, **1** and **2** displaced [$^3$H]KA from cortical membrane proteins with $IC_{50}$ (half maximal inhibitory concentration) values of approximately 10 μM and 4.9 ± 2.3 μM, respectively.[5] In addition, the biological action of **1** and **2** on GABA receptors has not yet been studied because of the limited availability from natural resources. We anticipated that de novo synthetic modifications of **1** and **2** would generate a more robust source of the analogs and facilitate new biological studies with these unusual molecules. In

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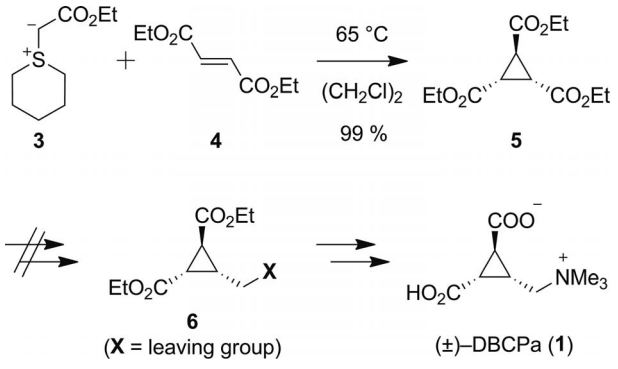
2007, the first synthesis of DBCPa (**1**) in its racemic form was reported by Donaldson et al.[12] This synthesis featured the formation of the cyclopropane ring, starting from a reaction between a [(pentadienyl)iron]$^{1+}$ cation and nitromethane anion, and successfully confirmed the relative stereochemistry of **1**. However, the synthesis was not practical in terms of the preparation of pure specimens of structural analogs, which are necessary for detailed biological evaluations. Herein, we report the synthesis of racemic DBCPa (**1**),[13] which will then extend to its asymmetric synthesis to determine its absolute stereochemistry. Moreover, our synthetic route was capable of synthesizing five racemic analogs, as discussed below.

## Results and Discussion

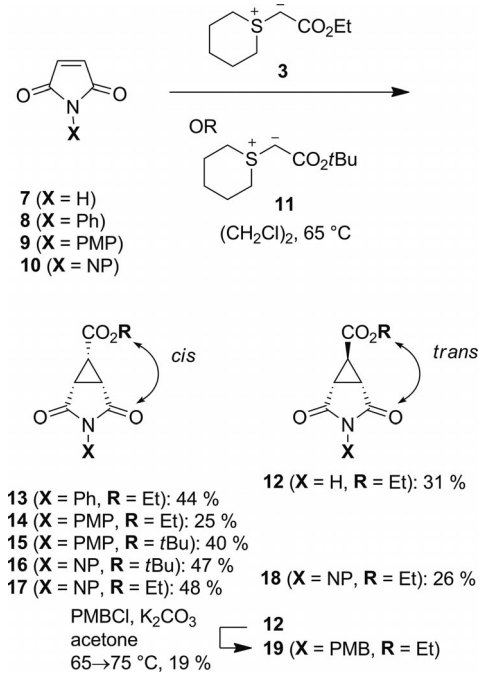
Several methods have been reported for the construction of 1,2-disubstituted cyclopropanes to prepare cyclopropane-containing GABA analogs.[14] The key reactions include: (1) an intramolecular alkylative cyclization reaction[15] and (2) a diastereoselective cyclopropanation of β-hydroxy-γ,δ-unsaturated carbonyl compounds.[16] However, these methodologies are limited to 1,2-disubstituted cyclopropanes and not applicable to 1,2,3-trisubstituted cyclopropanes such as DBCPa (**1**) and DBCPb (**2**), which are the unique examples of 1,2,3-trisubstituted cyclopropanes found in natural products.[5] Although related compounds such as DCV-IV,[17] carene-derived analogs,[18] and some GABA analogs[19] have been generated previously, synthetic methods for entry into the 1,2,3-trisubstituted cyclopropane motif have not been well established.

In 2000, Aggarwal et al. reported the synthesis of *trans*-1,2,3-cyclopropanetricarboxylic acid triethyl ester (**5**) using sulfonium ylide **3** and diethyl fumarate (**4**, see Scheme 1).[20] Initially, we anticipated that **5** would serve as a key intermediate for the synthesis of **6**, which should be a direct precursor to DBCPa (**1**). However, upon several experiments, the transformation of **5** into **6** was not readily realized, because of the following: (1) the poor selectivity in the functional-group differentiation on **5** by alkaline or hydride treatment, for example, and (2) the epimerization observed under the reducing conditions.




Scheme 1. Our initial plan toward DBCPa (**1**) by way of known triester **5**.

Therefore, we explored the synthetic approach by using cyclic imides to accomplish the functional-group differentiation efficiently. Because substituents on the imide-nitrogen were expected to control the reactivity, we planned for the seven cyclopropane-fused succinimides (**12–17** and **19**) to use in our experiments and prepared them as shown in Scheme 2. Thus, the cyclopropanation of commercially available maleimide (**7**) and *N*-phenylmaleimide (**8**) along with the two synthetic maleimides **9** and **10**, prepared by the conventional two-step condensation of maleic anhydride and amines (AcOH; NaOAc, $Ac_2O$, 100 °C),[21] was carried out by using ethoxycarbonyl- and *tert*-butoxycarbonyl-substituted sulfonium ylides **3**[20] and **11** at 65 °C. Generally, *cis*-cyclopropanes **13–17** were obtained as the major products in moderate yields, along with *trans* isomers such as **18** as the minor products. The reaction with maleimide (**7**) was an exception, wherein *trans* isomer **12** was predominantly obtained in 31% yield. It should be noted that *N*-(4-nitrophenyl)maleimide (**10**) provided adduct **17** in the highest yield (48%), among the reactions with all of the maleimides **7–10**, probably owing to the electron-withdrawing nature of the 4-nitrophenyl group. The stereochemistry was determined on the basis of the results from a NOESY experiment on **17**, as shown in Figure 2, and was finally confirmed by transforming diastereomer **18** into dysibetaine CPa (**1,** see discussion below). All of the other products were assigned by analogy. The cyclopropanation of *N*-substituted maleimides **8–10** provided products in favor of the *cis* isomers over the *trans* isomers, and the stereoselectivities are in good agreement with previous observations.[22] *N*-PMB imide **19** with a *trans* configuration was synthesized (PMBCl, $K_2CO_3$) from *trans*-imide **12**.[23]




Scheme 2. Preparation of cyclopropane-fused succinimides. Abbreviations are PMP = 4-methoxyphenyl, NP = 4-nitrophenyl, and PMB = 4-methoxybenzyl.

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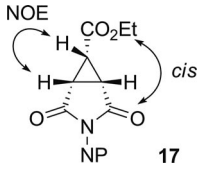


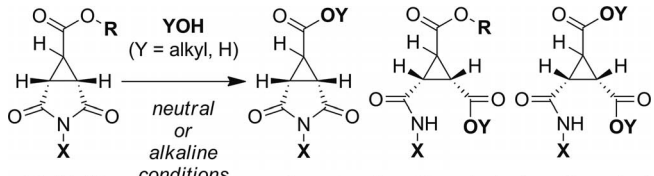

Figure 2. NOE observed in *cis*-cyclopropane **17** for determination of the stereochemistry.

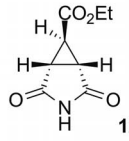
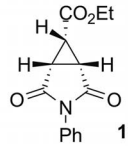
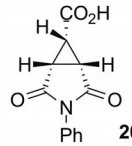
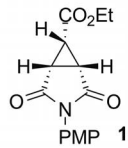
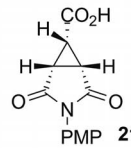
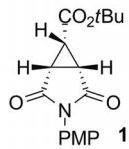
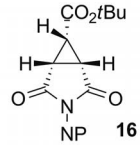
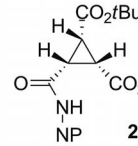
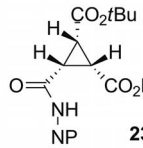
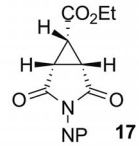
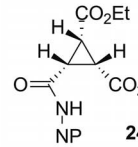
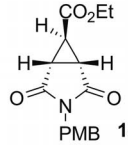
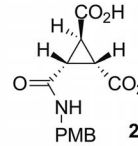
Attempts at the chemoselective alcoholysis or hydrolysis of the cyclic imide moiety in the presence of the ester functional group by using *cis*-cyclopropanes **13**–**17** and *trans*-cyclopropanes **12** and **19** are shown in Table 1. We postulated that *cis* isomers **13**–**17** would be especially well-suited as substrates for our model study, directed toward the total synthesis of dysibetaine CPa (**1**) and its analogs, because the *cis*-cyclopropane is sterically demanding and perhaps less reactive than the diastereomeric *trans*-cyclopropanes **12**, **18**, and **19**. In these experiments, we generally observed three types of products generated: (1) by solvolysis of the ester (type-**A**), (2) by opening of the cyclic imide (type-**B**, desired), and (3) by uncontrolled reactions at both sites (type-**C**).

As shown in Table 1, Entry 1, the simplest imido ester **12** decomposed upon hydrolysis (NaOH, MeOH, $H_2O$). Hydrolysis of *N*-phenylimido ester **13** provided the undesired carboxylic acid **20A** in 76% yield, showing that the ester functionality is more reactive than the *N*-phenylimide moiety (see Table 1, Entry 2). The same selectivity was also observed with 4-methoxyphenyl derivative **14** under mild conditions (LiOH, MeOH, $H_2O$, –10 °C), which cleanly gave undesired carboxylic acid **21A** in 93% yield (see Table 1, Entry 3). Changing the ester to the sterically demanding *tert*-butyl ester **15** only resulted in decomposition and did not improve the selectivity (see Table 1, Entry 4). After several experiments, the desired selectivity was first observed with *N*-(4-nitrophenyl)imido ester **16**, which underwent hydrolysis predominantly at the imide functionality by using LiOH and $H_2O$ at 0 °C to provide carboxylic acid **22B** in 77% yield (see Table 1, Entry 5). *N*-NP imido ester **16** not only underwent hydrolysis but also underwent methanolysis, both proceeding chemoselectively even under neutral conditions. As shown in Table 1, Entry 6, methanolysis at 100 °C (sealed tube) or under microwave irradiation (ca. 120 °C) without any additives gave the desired methyl ester **23B** in 66% yield. Not surprisingly, alcoholysis with the bulkier EtOH resulted in diminished reactivity, and an amine additive ($Et_3N$) was required for the reaction to proceed (**17** → **24B**, see Table 1, Entry 7). The reactivity of the imide was lower in *trans*-substituted cyclopropane **19** bearing the *N*-PMB imide, and dicarboxylic acid **25C** was formed in 60% yield, resulting in hydrolysis (NaOH, MeOH, $H_2O$, 0 °C) of both the ester and imide functionalities (see Table 1, Entry 8). In all of the entries, the cyclopropane ring was stable and unaffected during the reaction.

Next, as a preliminary model study toward the synthesis of DBCPa (**1**), the transformation of amide **24B** was examined (see Scheme 3). Treatment of the amide with $Boc_2O$ (Boc = *tert*-butoxycarbonyl) in the presence of $Et_3N$ and DMAP [4-(*N*,*N*-dimethylamino)pyridine] provided *N*-Boc imide **26** in excellent yield (97%). However, to our disap-

Table 1. Initial attempts for chemoselective reaction of cyclic imide over ester functional group.




| Entry | Substrate | Conditions | Product | Yield |
|---|---|---|---|---|
| 1 |  **12** | NaOH MeOH $H_2O$, r.t. | dec. | – |
| 2 |  **13** | NaOH MeOH $H_2O$, r.t. |  **20A** | 76% |
| 3 |  **14** | LiOH MeOH $H_2O$ –10 °C |  **21A** | 93% |
| 4 |  **15** | NaOH MeOH $H_2O$, r.t. | dec. | – |
| 5 |  **16** | LiOH MeOH $H_2O$ 0 °C |  **22B** | 77% |
| 6 | **16** | MeOH 100 °C or microwave |  **23B** | 66% |
| 7 |  **17** | EtOH $Et_3N$ microwave |  **24B** | 32% |
| 8 |  **19** | NaOH MeOH $H_2O$ 0 °C |  **25C** | 60% |

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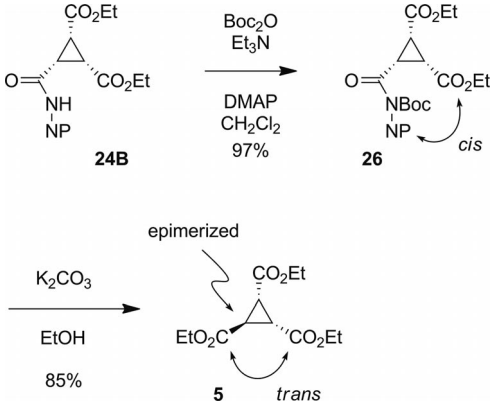
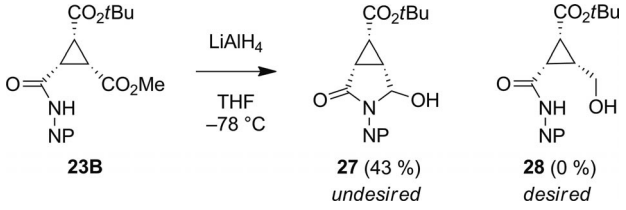
pointment, the ethanolysis of the *N*-Boc imide **26** gave as the sole product triethyl ester **5**[20] with the *trans* configuration in 85% yield. The epimerization was apparently a result of conducting the reaction under such thermodynamic reaction conditions, suggesting that the transformation of the 1,2,3-tricarbonylcyclopropane moiety should be carefully performed. Also, it should be noted that the *cis* isomer of **5** has not been reported to date, probably because of its instability,[20] and the synthesis still proves to be challenging.



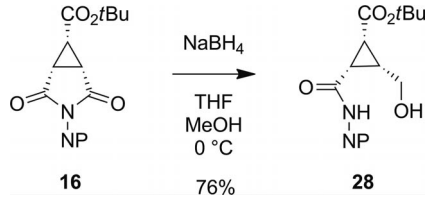

Scheme 3. Observed epimerization during reaction of *cis*-cyclopropane **26**.

Next, to avoid the undesired epimerization, shown in Scheme 3, the selective reduction of methyl ester **23B** was explored using $LiAlH_4$, to generate primary alcohol **28**. As shown in Scheme 4, **23B** was readily reduced at –78 °C, but the product was unexpected aminal **27** (43% yield). Although no epimerization was detected in the reduction, cyclic aminal **27** was not desirable as a synthetic intermediate for **28**, as extensive transformations would be additionally required.



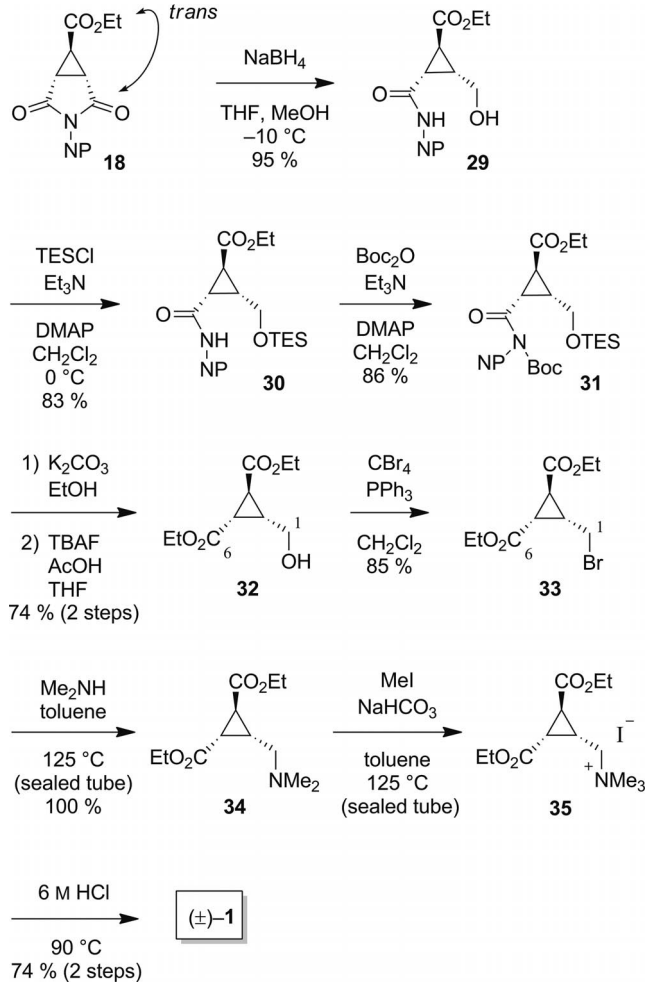

Scheme 4. Selective reduction of methyl ester **23B**.

We further investigated the selective reductions of the compounds listed in Table 1. After extensive experiments, *N*-NP imide **16** was eventually found to be a well-suited substrate, which was cleanly converted into amido alcohol **28**. The reduction of **16** with $NaBH_4$ in THF (tetrahydrofuran) and MeOH[24,25] was successfully realized in 76% yield, as shown in Scheme 5. No epimerization was detected, and **28** was obtained as a single isomer.[26]




Scheme 5. Successful reduction of cyclic imide **16** with $NaBH_4$.

Thus, the reduction of *N*-NP imide **16** by using $NaBH_4$ successfully gave us functional-group differentiation, resulting finally in the total synthesis of (±)-dysibetaine CPa (**1**). As shown in Scheme 6, *trans*-cyclopropane imide **18** was readily and regioselectively reduced with $NaBH_4$ at –10 °C to give amidoalcohol **29** in excellent yield (95%). As expected, the reactivity of imide **18** was higher than that of the *cis*-substituted cyclopropane **16** used in the model study (see Scheme 5). The hydroxy group of **29** was protected [TESCl (triethylsilyl chloride), $Et_3N$, DMAP, 83%], and then amide **30** was converted into imide **31** in 86% yield by treatment with $Boc_2O$, $Et_3N$, and DMAP. The alkaline ethanolysis of the *N*-Boc imide by using $K_2CO_3$ in EtOH successfully delivered the diethyl ester, which in turn, was




Scheme 6. Total synthesis of (±)-dysibetaine CPa (**1**) from *trans*-cyclopropane **18**.

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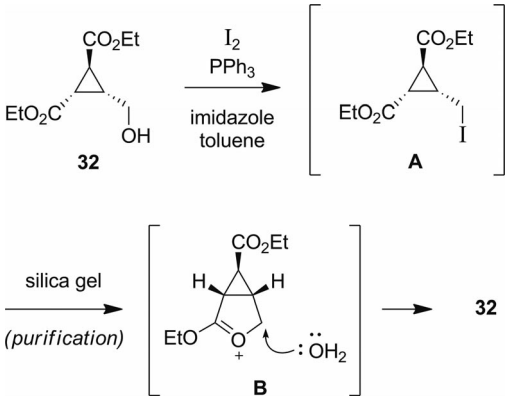
treated with tetra-*n*-butylammonium fluoride (TBAF) and AcOH to give alcohol **32** in 74% yield.

To introduce nitrogen functionality at C-1 of **32** (using the dysibetaine CPa numbering scheme), a two-step procedure by way of an iodide intermediate was first examined. Although the generation of an intermediary iodide (see Scheme 7, Intermediate **A**) was unequivocally confirmed by TLC and $^1$H NMR, the iodide was unstable and readily underwent hydrolysis during purification by silica gel column chromatography to give the recovered alcohol **32**. This likely occurred because of the involvement of the neighboring ethoxycarbonyl group (see Scheme 7, Intermediate **B**).

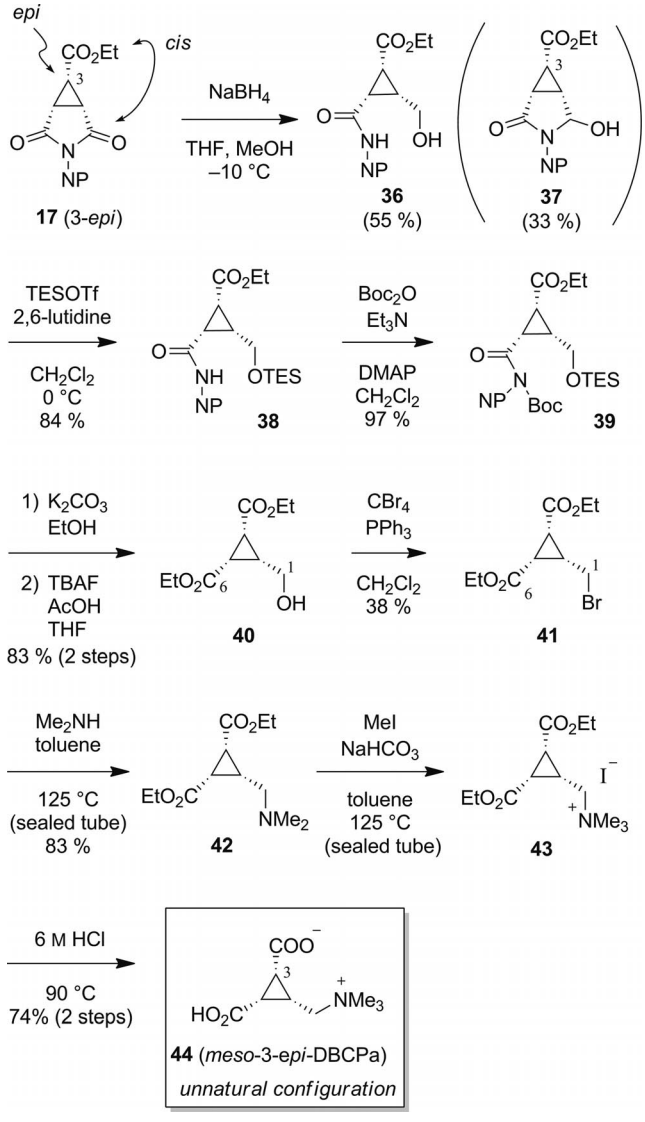



Scheme 7. Plausible reaction mechanism for unexpected hydrolysis of iodide **A** derived from **32**.

Fortunately, the corresponding bromide **33**, synthesized by treating **32** with $CBr_4$ and $PPh_3$, was stable and isolable in 85% yield (see Scheme 6). With bromide **33** in hand, we next constructed the quaternary ammonium salt by examining two methods: (1) a one-step introduction by using $Me_3N$[27,28] and (2) a two-step procedure by successive treatment with $Me_2NH$ and MeI.[29,30] In the former one-step method, bromide **33** did not react with $Me_3N$, even at an elevated temperature (125 °C), and **33** was recovered intact. On the other hand, the latter two-step reaction proved to be of value, as shown in Scheme 6 (**33** → **34** → **35**). Thus, treatment of bromide **33** with $Me_2NH$ in toluene at 125 °C in a sealed tube gave rise to tertiary amine **34** quantitatively, which was then further treated with $CH_3I$ at 125 °C (sealed tube) to provide quaternary ammonium iodide **35**. The addition of $NaHCO_3$ was essential to complete the reaction. These experiments indicated that the C-1 position is sterically shielded in comparison to muscarine, which bears an analogous trimethylammonium group, which is generally synthesized by using the one-step reaction with $Me_3N$.[27]

Without purification, **35** was hydrolyzed by treatment with 6 M hydrochloric acid at 90 °C to furnish (±)-dysibetaine CPa (**1**) in 74% yield. The synthetic specimen was identical to its natural counterpart chromatographically (TLC, HPLC) and spectroscopically ($^1$H and $^{13}$C NMR), thus confirming the stereochemical assignments of cyclopropanation products **17** and **18**.[31] The overall yield was 4.53% over a total of 12 steps, starting from maleic anhydride.

Starting from *cis*-cyclopropane **17**, the synthesis of a C-3 epimer of dysibetaine CPa was also accomplished. As shown in Scheme 8, the synthesis of *meso*-3-*epi*-dysibetaine CPa (**44**) was essentially identical to that for **1** (see Scheme 6), however, undesired side reactions were observed in two transformations. First, a substantial amount (33%) of 3-*epi*-aminal intermediate **37** was obtained in the reduction of imide **17** to afford **36** ($NaBH_4$, THF, MeOH, –10 °C). Attempts to complete the reaction were unsuccessful and resulted in over-reduction (data not shown). Second, after the alkaline ethanolysis of **39** ($K_2CO_3$, EtOH), a trace amount (<5%) of the epimerized product, identical to the ethanolysis product of *trans*-cyclopropane **31**, was detected. However, the byproduct could be successfully removed by silica gel column chromatography after the desilylation (TBAF, AcOH). The side reactions apparently took place because of the steric congestion of the *cis*-arranged substituents on the cyclopropane ring. Overall, *meso*-3-*epi*-




Scheme 8. Synthesis of *meso*-3-*epi*-dysibetaine CPa (**44**) from *cis*-cyclopropane **17**.

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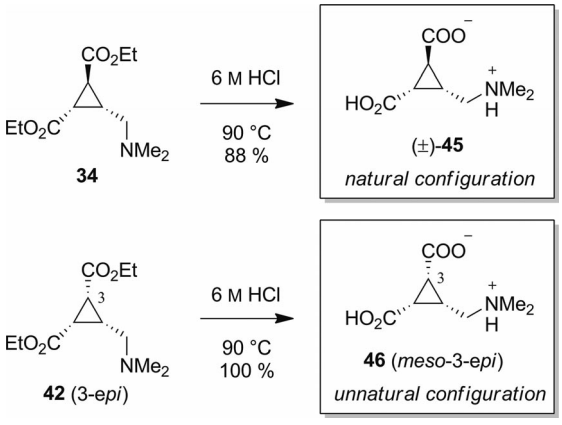
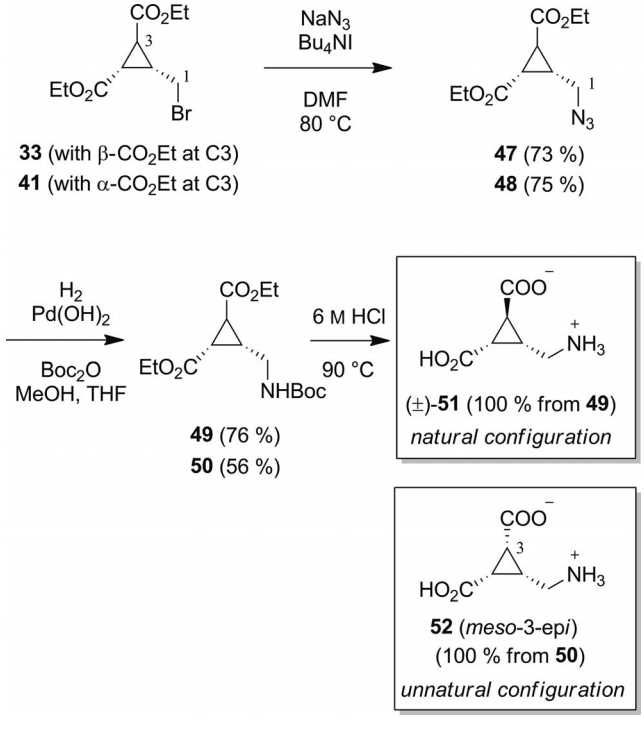
dysibetaine CPa (**44**) was synthesized in a total 2.59% yield over 12 steps starting from maleic anhydride.

Tertiary ammonium analogs with natural and unnatural configurations were synthesized by acidic hydrolysis starting from the synthetic intermediates **34** and **42** (3-*epi*), respectively (see Scheme 9). Thus, (±)-**45** with the natural configuration was obtained in 88% yield, and **46** with the unnatural configuration was furnished quantitatively. The overall yields were 5.39% (for **45**) and 3.50% (for **46**) with a total of 11 steps each, starting from maleic anhydride.




Scheme 9. Synthesis of tertiary ammonium analogs (±)-**45** and **46** (*meso*-3-*epi*).

Scheme 10 depicts the syntheses of *N*-desmethyl analogs (±)-**51** and **52** (*meso*-3-*epi*) starting from bromides **33** and **41**, respectively. The introduction at the C-1 position of an azide group, as an amino group precursor, proceeded smoothly at 80 °C by using $NaN_3$ and $Bu_4NI$ in DMF (dimethylformamide) to give **47** (73%) and **48** (75%). The hydrogenolysis of the azide followed by *N*-Boc protection was attained in a one-pot reaction,[32] giving rise to *N*-Boc amine **49** and **50** in 76% and 56% yields, respectively. It should be noted that attempts to isolate the intermediate amine lowered the two-step yields to less than 10%, and hence, the in-situ *N*-Boc protection was essential. Finally, using the same hydrolysis procedure as was employed with the other analogs (i.e., **1**, **44**, **45**, and **46**), **49** and **50** were deprotected to furnish *N*-desmethyl analogs (±)-**51** and **52** (*meso*-3-*epi*), both in quantitative yields. The overall yields for **51** and **52** were 4.00% and 1.77%, respectively, with a total of 12 steps each, starting from maleic anhydride.




Scheme 10. Synthesis of *N*-desmethyl analogs (±)-**51** and **52** (*meso*-3-*epi*).

## Conclusions

In conclusion, we have successfully synthesized dysibetaine CPa (DBCPa, **1**), a cyclopropane carboxylic acid bearing a quaternary ammonium group, found in the Micronesian marine sponge *L. chondrodes*,[5] in its racemic form. The de novo synthesis was performed in 2.59% yield over a total of 12 steps starting from maleic anhydride and was accomplished by taking advantage of the electron-withdrawing *N*-(4-nitrophenyl) group used in the cyclopropanation reaction (**10** → **17** + **18**, 74% total), the reductive ring opening of the imide (**18** → **29**, 95%), and the ethanolysis of the *N*-Boc imide (**31** → **32**, >74%).[13] This synthetic route was capable of providing five analogs that are stereoisomers and isomers bearing different ammonium group patterns. To clarify their structure–activity relationships, the evaluation of their biological activities toward neuronal receptors is in progress. An asymmetric synthesis is also being studied in our laboratory to determine the absolute stereochemistry of these compounds as well as develop selective ligands. Our present study affords synthetic strategies toward this goal.[33]

## Experimental Section

**General Methods:** All reactions susceptible to moisture and air were carried out in an atmosphere of argon gas, in glassware oven-dried for 3 h, and in solvents freshly distilled from sodium and benzophenone. Tetrahydrofuran and *N*-phenylmaleimide (**8**) were purchased from Wako Pure Chemical Industries. All of the other chemicals were purchased at the highest commercial grade and used directly. The experiments by microwave irradiations were carried out using the oven, as reported by Arai et al.[34] Analytical thin-layer chromatography (TLC) was performed using Merck silica gel 60 F254 plates (0.25-mm thickness). Flash column chromatography was carried out using Merck silica gel 60 (230–400 mesh) or Fuji Silicia silica gel BW-300 (200–400 mesh). Reversed-phase silica gel column chromatography was carried out using Fuji Silicia Chromatorex DM1020T (0.10-mm thickness). For high performance liquid chromatography (HPLC), the recycling preparative system LC-918 (Japan Analytical Industries) was used. The IR spectra were recorded with a Perkin–Elmer Spectrum One FTIR spectrometer. $^1H$ and $^{13}C$ NMR spectroscopic data were recorded with a BRUKER AVANCE 400 spectrometer. The chemi-

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cal shift values are reported in $\delta$ (ppm) with a reference to the internal residual solvent [$^1$H NMR, $CDCl_3$ (7.24), $D_2O$ (4.70), [$D_6$]-DMSO (2.62); $^{13}$C NMR, $CDCl_3$ (77.0), [$D_6$]DMSO (40.5)]. The coupling constants ($J$) are reported in Hertz (Hz). The abbreviations used to designate the multiplicities are s singlet, d doublet, t triplet, q quartet, m multiplet, and br. broad. ESI-TOF mass spectra were measured with a Water LCT Premier XE spectrometer.

**Ethyl Pentamethylene-λ$^4$-sulfanylideneacetate (3):**[20] To a stirred solution of pentamethylene sulfide (2.750 g, 26.9 mmol) in acetone (4.5 mL) at room temp. was added ethyl bromoacetate (2.880 mL, 26.9 mmol). After 47 h, the resulting solid was collected by filtration and washed with cold acetone (5 mL) to give the crude (ethoxycarbonylmethyl)pentamethylenesulfonium bromide (6.50 g) as a white solid, which was used without purification in the next reaction. To a stirred solution of the crude sulfonium bromide (6.50 g) in $CHCl_3$ (27.0 mL) at 0 °C were added saturated aqueous $K_2CO_3$ (9.2 mL) and aqueous NaOH (50% w/v, 2.0 mL). After stirring at room temp. for 20 min, the mixture was filtered through a pad of Celite by using $CHCl_3$. The filtrate was dried with $Na_2SO_4$ and concentrated under reduced pressure to give ylide **3** (4.500 g, 89% for 2 steps) as a colorless oil, which was used without purification in the next reaction; $R_f$ = 0.58 ($t$BuOH/AcOH/$H_2O$, 33:33:33). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.02 (t, $J$ = 7.2 Hz, 2 H), 3.61 (br., 2 H), 3.01 (br., 1 H), 2.75 (d, $J$ = 11.2 Hz, 2 H), 2.10 (d, $J$ = 13.6 Hz, 2 H), 1.77–1.65 (m, 3 H), 1.42 (dd, $J$ = 13.6, 11.2 Hz, 1 H), 1.20 (t, $J$ = 7.2 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 170.2, 57.9, 44.9 (2×), 33.0, 24.2, 23.6 (2×), 14.9 ppm. The other spectroscopic data were in good agreement with those reported.[20]

***N*-(4-Methoxyphenyl)maleimide (9):** According to the original procedure for the synthesis of *N*-phenylmaleimide (**8**) reported by Cava et al.,[21] *N*-(4-methoxyphenyl)maleimide (**9**) was prepared. To a stirred solution of maleic anhydride (700.0 mg, 7.14 mmol) in acetic acid (70 mL) at room temp. was added 4-methoxyaniline (*p*-anisidine, 879.0 mg, 7.14 mmol). After 100 min, the mixture was concentrated under reduced pressure by coevaporation with toluene (2×) to give the crude maleic acid mono(4-methoxyphenyl)amide (1.591 g) as a yellow solid, which was used without purification in the next reaction. A solution of the crude maleic acid mono(4-methoxyphenyl)amide (1.300 g) and AcONa (241.1 mg, 2.94 mmol) in $Ac_2O$ (2.7 mL) was heated to 100 °C with stirring. After 4 h, the hot mixture was poured onto ice (20 g). After the ice melted, the mixture was diluted with EtOAc (100 mL) and $H_2O$ (50 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (20 mL), and the combined extracts were washed with brine (20 mL), dried with $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30 g, EtOAc/hexane, 15:85) to give *N*-(4-methoxyphenyl)-maleimide (**9**, 950.0 mg, 79%) as a yellow solid; $R_f$ = 0.51 (EtOAc/hexane, 40:60). The spectroscopic data were in good agreement with those reported.[35]

***N*-(4-Nitrophenyl)maleimide (10):** Using the same procedure for the synthesis of **9**, **10** was prepared in a reasonable yield. Thus, to a stirred solution of maleic anhydride (400.0 mg, 4.08 mmol) in acetic acid (40.0 mL) at room temp. was added 4-nitroaniline (563.4 mg, 4.08 mmol). After 1.5 h, the mixture was concentrated under reduced pressure to give the crude maleic acid mono(4-nitrophenyl)-amide (962.0 mg) as a yellow solid. The residue was used without purification in the next reaction. Selected data for the intermediary amide: $R_f$ = 0.60 (EtOAc/hexane, 50:50). IR (KBr): $\tilde{\nu}$ = 3298, 3089, 1707, 1515, 1338, 1308, 1274, 1112 cm$^{-1}$. $^1$H NMR (400 MHz, [$D_6$]DMSO): $\delta$ = 8.25 (d, $J$ = 9.2 Hz, 2 H), 7.87 (d, $J$ = 9.2 Hz, 2 H), 6.53 (d, $J$ = 12.0 Hz, 1 H), 6.38 (d, $J$ = 12.0 Hz, 1 H) ppm. $^{13}$C NMR (100 MHz, [$D_6$]DMSO): $\delta$ = 168.0, 165.1, 145.8, 143.4, 132.4, 131.1, 126.0 (2×), 120.1 (2×) ppm. HRMS (ESI): calcd. for $C_{10}H_9N_2O_5^+$ [M + H]$^+$ 237.0511; found 237.0517. A solution of the crude maleic acid mono(4-nitrophenyl)amide (962.0 mg) and AcONa (166.7 mg, 2.03 mmol) in $Ac_2O$ (5.8 mL) was heated to 100 °C with stirring. After 4 h, the hot mixture was poured onto ice (10 g). After the ice melted, the mixture was diluted with $CHCl_3$ (20 mL), and the resulting mixture was washed with saturated aqueous $NH_4Cl$ (5 mL) and brine (5 mL), dried with $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10 g, EtOAc/hexane, 80:20) to give *N*-(4-nitrophenyl)maleimide (**10**, 581.1 mg, 65%) as a yellow solid; $R_f$ = 0.71 (acetone/$CHCl_3$, 10:90). IR (film): $\tilde{\nu}$ = 3099, 1724, 1599, 1505, 1343, 1143 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.31 (d, $J$ = 8.8 Hz, 2 H), 7.65 (d, $J$ = 8.8 Hz, 2 H), 6.91 (s, 2 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 168.5 (2×), 146.1, 137.0, 134.6 (2×), 125.5 (2×), 124.5 (2×) ppm. HRMS (ESI): calcd. for $C_{10}H_7N_2O_4^+$ [M + H]$^+$ 219.0406; found 219.0401. The other spectroscopic data were in good agreement with those reported.[36,37]

***tert*-Butyl Pentamethylene-λ$^4$-sulfanylideneacetate (11):** To a stirred solution of pentamethylene sulfide (700.0 mg, 6.85 mmol) in acetone (1.05 mL) at room temp. was added *tert*-butyl bromoacetate (1.010 mL, 6.85 mmol). After stirring at room temp. for 75 h, the resulting solid was collected by filtration, washed with cold acetone (5 mL), and dried under air to give the crude (*tert*-butoxycarbonylmethyl)pentamethylenesulfonium bromide (1.800 g, 90%) as a white solid, which was pure enough to be used in the next reaction without any further purification; $R_f$ = 0.42 ($t$BuOH/AcOH/$H_2O$, 33:33:33). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 5.21 (s, 2 H), 4.40 (br., 2 H), 3.85 (br. d, $J$ = 10.4 Hz, 2 H), 2.26 (br. d, $J$ = 13.6 Hz, 2 H), 1.94–1.79 (m, 4 H), 1.46 (s, 9 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 163.4, 86.0, 43.5, 36.1 (2×), 27.9 (3×), 22.6 (2×), 22.4 ppm. To a stirred solution of the sulfonium bromide (290.0 mg, 0.989 mmol) in $CHCl_3$ (1.2 mL) at 0 °C were added saturated aqueous $K_2CO_3$ (0.866 mL) and aqueous NaOH (50% w/v, 0.116 mL). After stirring at room temp. for 20 min, the mixture was filtered through a pad of Celite by using $CHCl_3$. The filtrate was dried with $Na_2SO_4$ and concentrated under reduced pressure to give ylide **11** (214.0 mg, 100%) as a colorless oil, which was used without purification in the next reaction; $R_f$ = 0.64 ($t$BuOH/AcOH/$H_2O$, 33:33:33). IR (film): $\tilde{\nu}$ = 3410, 2938, 2860, 1624, 1437, 1345, 1134, 836, 752 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 3.43 (dd, $J$ = 13.6, 11.0 Hz, 2 H), 2.93 (br., 1 H), 2.70 (br. d, $J$ = 11.0 Hz, 2 H), 2.02 (br. d, $J$ = 13.6 Hz, 2 H), 1.71–1.58 (m, 4 H), 1.39 (s, 9 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 170.5, 76.7, 42.4 (2×), 34.9, 29.0 (3×), 24.0 (2×), 23.8 ppm. HRMS (ESI): calcd. for $C_{11}H_{21}O_2S^+$ [M + H]$^+$ 217.1262; found 217.1257.

**Ethyl (1*R**,5*S**,6*r**)-2,4-Dioxo-3-azabicyclo[3.1.0]hexane-6-carboxylate (12):** To a stirred solution of ylide **3** (69.9 mg, 0.372 mmol) in 1,2-dichloroethane (0.744 mL) at 50 °C was added maleimide (**7**, 108.3 mg, 1.11 mmol). After 100 min, the mixture was filtered through a pad of Celite by using $CHCl_3$. The filtrate was concentrated, and the resulting residue was purified by column chromatography on silica gel (7.5 g, EtOAc/hexane, 80:20) to give *trans*-cyclopropane **12** (20.9 mg, 31%) as a yellow oil; $R_f$ = 0.40 (EtOAc/hexane, 40:60). IR (film): $\tilde{\nu}$ = 3353, 1718, 1350, 1314, 1277, 1197, 1034, 921, 807 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.15 (br., 1 H), 4.19 (q, $J$ = 7.2 Hz, 2 H), 2.85 (dd, $J$ = 2.8, 1.6 Hz, 2 H), 2.52 (dd, $J$ = 2.8, 2.8 Hz, 1 H), 1.27 (t, $J$ = 7.2 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.8 (2×), 167.3, 62.3, 32.0, 27.7 (2×) ppm. HRMS (ESI): calcd. for $C_8H_{10}NO_4^+$ [M + H]$^+$

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184.0610; found 184.0605. The stereochemistry of **12** was determined to be *trans* by comparing the $^1$H NMR spectroscopic data with those of *trans*-cyclopropane **18**.

**Ethyl (1*R**,5*S**,6*s**)-2,4-Dioxo-3-phenyl-3-azabicyclo[3.1.0]hexane-6-carboxylate (13):** According to the same procedure for the synthesis of **12**, *N*-phenylmaleimide (**8**, 69.1 mg, 0.399 mmol) and ylide **3** (50.0 mg, 0.266 mmol) gave *cis*-cyclopropane **13** (30.0 mg, 44%) as a colorless oil; $R_f$ = 0.40 (EtOAc/hexane, 40:60). IR (film): $\tilde{\nu}$ = 3080, 2983, 1715, 1598, 1501, 1387, 1300, 1189, 869, 758, 694 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.44–7.31 (m, 5 H), 4.18 (q, $J$ = 8.0 Hz, 2 H), 2.93 (d, $J$ = 8.4 Hz, 2 H), 2.64 (dd, $J$ = 8.4, 8.4 Hz, 1 H), 1.24 (t, $J$ = 8.0 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 170.4, 167.3, 131.5, 129.0 (2×), 128.5, 128.3, 126.5 (2×), 62.3, 31.5, 26.8 (2×), 14.0 ppm. HRMS (ESI): calcd. for $C_{14}H_{14}NO_4^+$ [M + H]$^+$ 260.0923; found 260.0916.

**Ethyl (1*R**,5*S**,6*s**)-3-(4-Methoxyphenyl)-2,4-dioxo-3-azabicyclo-[3.1.0]hexane-6-carboxylate (14):** According to the same procedure for the synthesis of **12**, *N*-(4-methoxyphenyl)maleimide (**9**, 86.4 mg, 0.425 mmol) and ylide **3** (100.0 mg, 0.532 mmol) gave *cis*-cyclopropane **14** (28.7 mg, 25%) as a colorless oil; $R_f$ = 0.36 (EtOAc/hexane, 50:50). IR (film): $\tilde{\nu}$ = 3078, 2917, 1713, 1515, 1392, 1300, 1251, 1190, 1066, 1033, 832 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.23 (d, $J$ = 8.8 Hz, 2 H), 6.94 (d, $J$ = 8.8 Hz, 2 H), 4.18 (q, $J$ = 7.2 Hz, 2 H), 3.79 (s, 3 H), 2.92 (d, $J$ = 8.0 Hz, 2 H), 2.62 (dd, $J$ = 8.0, 8.0 Hz, 1 H), 1.24 (t, $J$ = 7.2 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 170.7 (2×), 167.3, 159.4, 127.8 (2×), 124.2, 114.5 (2×), 62.2, 55.4, 31.5, 26.7 (2×), 14.0 ppm. HRMS (ESI): calcd. for $C_{15}H_{16}NO_5^+$ [M + H]$^+$ 290.1028; found 290.1024.

***tert*-Butyl (1*R**,5*S**,6*s**)-3-(4-Methoxyphenyl)-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carboxylate (15):** According to the same procedure for the synthesis of **12**, *N*-(4-methoxyphenyl)maleimide (**9**, 40.4 mg, 0.199 mmol) and ylide **11** (53.8 mg, 0.249 mmol) gave *cis*-cyclopropane **15** (25.6 mg, 40%) as a colorless oil; $R_f$ = 0.28 (EtOAc/hexane = 30:70). IR (film): $\tilde{\nu}$ = 3376, 2922, 2855, 1645, 1578, 1133, 767 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.22 (d, $J$ = 9.2 Hz, 2 H), 6.94 (d, $J$ = 9.2 Hz, 2 H), 3.79 (s, 3 H), 2.86 (d, $J$ = 8.0 Hz, 2 H), 2.59 (dd, $J$ = 8.0, 8.0 Hz, 1 H), 1.42 (s, 9 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.0, 166.0, 159.4, 128.3, 127.9 (2×), 124.2, 114.4 (2×), 83.3, 55.4, 32.0, 27.9 (3×), 26.5 (2×) ppm. HRMS (ESI): calcd. for $C_{17}H_{20}NO_5^+$ [M + H]$^+$ 318.1341; found 318.1336.

***tert*-Butyl (1*R**,5*S**,6*s**)-3-(4-Nitrophenyl)-2,4-dioxo-3-azabicyclo-[3.1.0]hexane-6-carboxylate (16):** According to the same procedure for the synthesis of **12**, *N*-(4-nitrophenyl)maleimide (**10**, 279.0 mg, 1.28 mmol) and ylide **11** (559.9 mg, 2.56 mmol) gave *cis*-cyclopropane **16** (200.7 mg, 47%) as a colorless oil; $R_f$ = 0.67 (acetone/$CHCl_3$, 10:90). IR (film): $\tilde{\nu}$ = 3283, 2917, 2850, 1639, 1567, 1540, 1416, 1133, 1094, 772 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.29 (d, $J$ = 8.0 Hz, 2 H), 7.58 (d, $J$ = 8.0 Hz, 2 H), 2.94 (d, $J$ = 8.0 Hz, 2 H), 2.65 (dd, $J$ = 8.0, 8.0 Hz, 1 H), 1.40 (s, 9 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 169.8 (2×), 166.0, 162.6, 137.2, 128.6 (2×), 124.2 (2×), 83.8, 32.8, 27.9 (3×), 26.8 (2×) ppm. HRMS (ESI): calcd. for $C_{16}H_{17}N_2O_6^+$ [M + H]$^+$ 333.1087; found 333.1092.

**Ethyl (1*R**,5*S**,6*s**)-3-(4-Nitrophenyl)-2,4-dioxo-3-azabicyclo-[3.1.0]hexane-6-carboxylate (17) and Ethyl (1*R**,5*S**,6*r**)-3-(4-Nitrophenyl)-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carboxylate (18):** To a stirred solution of ylide **3** (270.0 mg, 1.24 mmol) in 1,2-dichloroethane (37 mL) at 65 °C was added *N*-(4-nitrophenyl)maleimide (**10**, 349.1 mg, 1.24 mmol). After 1 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (7.5 g, EtOAc/hexane, 80:20) to give *cis*-cyclopropane **17** (182.4 mg, 48%) and *trans*-cyclopropane **18** (97.9 mg, 26%) as yellow oils. The stereochemistry of **17** and **18** was assigned on the basis of the results from a NOESY analysis, as discussed in the text (see Figure 2). Data for *cis*-cyclopropane **17**: $R_f$ = 0.21 (EtOAc/hexane, 40:60). IR (film): $\tilde{\nu}$ = 2992, 1746, 1694, 1520, 1349, 1313, 1198 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.28 (d, $J$ = 9.2 Hz, 2 H), 7.58 (d, $J$ = 9.2 Hz, 2 H), 4.17 (q, $J$ = 7.2 Hz, 2 H), 2.99 (d, $J$ = 8.4 Hz, 2 H), 2.68 (dd, $J$ = 8.4, 8.4 Hz, 1 H), 1.23 (t, $J$ = 7.2 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 169.5 (2×), 167.3, 146.7, 137.1, 127.0 (2×), 124.2 (2×), 62.4, 31.3, 27.0 (2×), 13.9 ppm. HRMS (ESI): calcd. for $C_{14}H_{13}N_2O_6^+$ [M + H]$^+$ 305.0774; found 305.0768. Data for *trans*-cyclopropane **18**: $R_f$ = 0.59 (EtOAc/hexane, 40:60). IR (film): $\tilde{\nu}$ = 2989, 1721, 1684, 1521, 1352, 1292, 1212 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.29 (d, $J$ = 8.8 Hz, 2 H), 7.49 (d, $J$ = 8.8 Hz, 2 H), 4.23 (q, $J$ = 7.2 Hz, 2 H), 3.07 (d, $J$ = 2.8 Hz, 2 H), 2.62 (dd, $J$ = 2.8, 2.8 Hz, 1 H), 1.30 (t, $J$ = 7.2 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 170.4 (2×), 166.8, 146.8, 136.6, 126.5 (2×), 124.4 (2×), 62.5, 31.8, 26.5 (2×), 14.1 ppm. HRMS (ESI): calcd. for $C_{14}H_{13}N_2O_6^+$ [M + H]$^+$ 305.0774; found 305.0771.

**Ethyl (1*R**,5*S**,6*r**)-3-(4-Methoxybenzyl)-2,4-dioxo-3-azabicyclo-[3.1.0]hexane-6-carboxylate (19):** To a stirred solution of imide **12** (20.0 mg, 0.109 mmol) and $K_2CO_3$ (15.1 mg, 0.109 mmol) in acetone (0.18 mL) at 65 °C was added 4-methoxybenzyl chloride (0.296 mL, 0.218 mmol). After 1 h, the temperature was raised to 75 °C, and the stirring was continued for 15 h. $H_2O$ (0.5 mL) was added, and the mixture was extracted with EtOAc (3 × 2 mL). The combined organic extracts were washed with brine (1 mL) and dried with $Na_2SO_4$. The residue was purified by column chromatography on silica gel (2 g, EtOAc/benzene, 10:90) to give PMB ether **19** (6.4 mg, 19%) as a yellow oil; $R_f$ = 0.55 (EtOAc/hexane, 40:60). IR (film): $\tilde{\nu}$ = 3083, 2955, 1711, 1514, 1393, 1248, 1193, 1035 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.22 (d, $J$ = 8.8 Hz, 2 H), 6.80 (d, $J$ = 8.8 Hz, 2 H), 4.42 (s, 2 H), 4.12 (m, 2 H), 3.79 (s, 3 H), 2.82 (d, $J$ = 2.8 Hz, 2 H), 2.22 (dd, $J$ = 2.8, 2.8 Hz, 1 H), 1.24 (m, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 172.0 (2×), 167.3, 159.3, 130.1 (2×), 129.4, 128.6, 114.2 (2×), 62.1, 55.2, 41.4, 32.1, 27.6, 14.0 ppm. HRMS (ESI): calcd. for $C_{16}H_{18}NO_5^+$ [M + H]$^+$ 304.1185; found 304.1188.

**(1*R**,5*S**,6*s**)-2,4-Dioxo-3-phenyl-3-azabicyclo[3.1.0]hexane-6-carboxylic Acid (20A):** To a stirred solution of ethyl ester **13** (100.0 mg, 0.386 mmol) in MeOH (0.808 mL) at room temp. was added a solution of NaOH (95.6 mg, 2.39 mmol) in $H_2O$ (0.400 mL). After 40 min, EtOAc (2 mL) and hydrochloric acid (1 M solution, 2 mL) were added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (1.5 mL). The combined organic extracts were concentrated under reduced pressure to give the crude carboxylic acid **20A** (67.7 mg, 76%) as a colorless solid, which was sufficiently pure for characterization; $R_f$ = 0.42 (EtOAc/MeOH/AcOH, 70:25:5). IR (film): $\tilde{\nu}$ = 3311, 2556, 1711, 1589, 1495, 1200, 1011 cm$^{-1}$. $^1$H NMR (400 MHz, $D_2O$): $\delta$ = 7.30–7.26 (m, 4 H), 7.12–7.11 (m, 1 H), 2.49 (dd, $J$ = 9.6, 9.6 Hz, 1 H), 2.30 (d, $J$ = 9.6 Hz, 2 H) ppm. $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ = 170.5 (2×), 166.6, 137.4, 127.8 (2×), 123.6, 119.4 (2×), 27.0, 24.9 (2×) ppm. HRMS (ESI): calcd. for $C_{12}H_8NO_4^-$ [M – H]$^-$ 230.0453; found 230.0458.

**(1*R**,5*S**,6*s**)-3-(4-Methoxyphenyl)-2,4-dioxo-3-azabicyclo-[3.1.0]hexane-6-carboxylic Acid (21A):** To a stirred solution of ethyl ester **14** (4.5 mg, 0.015 mmol) in MeOH (0.175 mL) and $H_2O$ (0.175 mL) at –10 °C was added a solution of LiOH (6.3 mg, 0.031 mmol) in MeOH (0.05 mL) and $H_2O$ (0.05 mL). After 25 min, the mixture was diluted with $CHCl_3$ (0.5 mL), and the resulting solution was extracted with $H_2O$ (3 × 0.5 mL). The com-

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bined aqueous layers were acidified with hydrochloric acid (1 M, solution, 1 mL), and the resulting solution was extracted with EtOAc (5 × 4 mL). The combined organic extracts were dried with $Na_2SO_4$ and concentrated under reduced pressure to give crude carboxylic acid **21A** (3.7 mg, 93%) as a colorless solid, which was sufficiently pure for characterization; $R_f$ = 0.39 (EtOAc/MeOH/AcOH, 60:35:5). IR (film): $\tilde{\nu}$ = 3022, 2547, 1710, 1505, 1245 $cm^{-1}$. $^1H$ NMR (400 MHz, $CD_3OD$): $\delta$ = 7.41 (d, $J$ = 8.6 Hz, 2 H), 6.85 (d, $J$ = 8.6 Hz, 2 H), 3.75 (s, 3 H), 2.56–2.47 (m, 3 H) ppm. $^{13}C$ NMR (100 MHz, $CD_3OD$): $\delta$ = 173.8 (2×), 169.5, 159.2, 133.3, 124.2 (2×), 115.9 (2×), 62.5, 29.7, 28.1 (2×) ppm. HRMS (ESI): calcd. for $C_{13}H_{10}NO_5^-$ $[M - H]^-$ 260.0559; found 260.0562.

**(1*R**,2*S**,3*S**)-2-(*tert*-Butoxycarbonyl)-3-[(4-nitrophenyl)carbamoyl]cyclopropanecarboxylic Acid (22B):** According to the same procedure for the synthesis of **21A**, *N*-(4-nitrophenyl)imide **16** (15.0 mg, 0.0451 mmol) at 0 °C gave carboxylic acid **22B** (12.2 mg, 77%) as a colorless oil; $R_f$ = 0.39 (EtOAc/MeOH/AcOH, 65:30:5). IR (film): $\tilde{\nu}$ = 3278, 2916, 2844, 1540, 1339, 1217, 773, 668 $cm^{-1}$. $^1H$ NMR (400 MHz, $D_2O$): $\delta$ = 8.14 (d, $J$ = 9.2 Hz, 2 H), 7.59 (d, $J$ = 9.2 Hz, 2 H), 2.43 (dd, $J$ = 9.6, 9.2 Hz, 1 H), 2.32 (dd, $J$ = 9.6, 9.2 Hz, 1 H), 2.13 (dd, $J$ = 9.6, 9.2 Hz, 1 H), 1.10 (s, 9 H) ppm. $^{13}C$ NMR (100 MHz, $D_2O$): $\delta$ = 174.2, 170.7, 169.8, 143.6, 143.3, 125.2 (2×), 119.7 (2×), 83.5, 30.3, 28.7, 27.0 (3×), 24.3 ppm. HRMS (ESI): calcd. for $C_{16}H_{17}N_2O_7^-$ $[M - H]^-$ 349.1036; found 349.1039.

**1-*tert*-Butyl 2-Methyl (1*S**,2*R**,3*S**)-3-[(4-Nitrophenyl)carbamoyl]-cyclopropane-1,2-dicarboxylate (23B):** A solution of *N*-(4-nitrophenyl)imide **16** (10.0 mg, 0.0301 mmol) in MeOH (1.0 mL) was heated to 100 °C in a sealed tube. After 12 h, the solution was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (2 g, EtOAc/benzene, 10:90) to give methyl ester **23B** (7.2 mg, 66%) as a colorless oil; $R_f$ = 0.52 (acetone/$CHCl_3$, 10:90). IR (film): $\tilde{\nu}$ = 3316, 2917, 2850, 1728, 1561, 1511, 1339, 1150, 1111, 850, 761 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 10.5 (br., 1 H), 8.30 (d, $J$ = 8.0 Hz, 2 H), 7.75 (d, $J$ = 8.0 Hz, 2 H), 3.73 (s, 3 H), 2.45–2.38 (m, 3 H), 1.40 (s, 9 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 170.0, 168.0, 164.9, 144.1, 143.3, 125.0 (2×), 119.2 (2×), 83.4, 52.8, 28.9, 27.8 (3×), 26.2, 25.0 ppm. HRMS (ESI): calcd. for $C_{17}H_{21}N_2O_7^+$ $[M + H]^+$ 365.1349; found 365.1358.

**Diethyl (1*R**,2*S**,3*r**)-3-[(4-Nitrophenyl)carbamoyl]cyclopropane-1,2-dicarboxylate (24B):** A solution of *N*-(4-nitrophenyl)imide **17** (40.5 mg, 0.133 mmol) and $Et_3N$ (0.090 mL) in EtOH (3.0 mL) was heated in a microwave oven (200 W) for 40 min. The mixture was diluted with $CHCl_3$ (10 mL), and the resulting solution was washed with saturated aqueous $NH_4Cl$ (3 mL) and brine (3 mL), dried with $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1 g, EtOAc/hexane, 60:40) to give diester **24B** (14.8 mg, 32%) as a yellow oil; $R_f$ = 0.36 (EtOAc/hexane, 50:50). IR (film): $\tilde{\nu}$ = 3338, 2987, 1733, 1597, 1511, 1342, 1302, 1189 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 10.50 (s, 1 H), 8.16 (d, $J$ = 9.2 Hz, 2 H), 7.74 (d, $J$ = 9.2 Hz, 2 H), 4.21–4.12 (m, 4 H), 2.48–2.45 (m, 3 H), 1.21 (t, $J$ = 6.8 Hz, 6 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 169.2 (2×), 164.8, 144.0, 143.0, 125.0 (2×), 119.2 (2×), 61.2 (2×), 29.0, 25.3 (2×), 14.0 (2×) ppm. HRMS (ESI): calcd. for $C_{16}H_{19}N_2O_7^+$ $[M + H]^+$ 351.1192; found 351.1187.

**(1*R**,2*R**)-3-[(4-Methoxybenzyl)carbamoyl]cyclopropane-1,2-dicarboxylic Acid (25C):** To a stirred solution of imido ester **19** (3.7 mg, 0.012 mmol) in MeOH (0.100 mL) at 0 °C was added a solution of NaOH (3.0 mg, 0.076 mmol) in $H_2O$ (0.012 mL). After 25 min, $H_2O$ (0.4 mL) and EtOAc (0.4 mL) were added. The aqueous layer was separated and acidified with hydrochloric acid (1 M solution, 0.5 mL). The resulting solution was extracted with EtOAc (0.4 mL), and the organic layer was dried with $Na_2SO_4$ and concentrated under reduced pressure to give the crude dicarboxylic acid **25C** (2.1 mg, 60%), which was sufficiently pure for characterization; $R_f$ = 0.73 (EtOAc/MeOH/AcOH, 60:35:5). IR (film): $\tilde{\nu}$ = 3020, 1523, 1424, 1044, 926 $cm^{-1}$. $^1H$ NMR (400 MHz, $D_2O$): $\delta$ = 7.14 (d, $J$ = 8.8 Hz, 2 H), 6.85 (d, $J$ = 8.8 Hz, 2 H), 4.19 (s, 2 H), 3.69 (s, 3 H), 2.45–2.38 (m, 2 H), 2.32 (m, 1 H) ppm. $^{13}C$ NMR (100 MHz, $D_2O$): $\delta$ = 176.0, 173.5, 169.6, 158.0, 134.0, 130.3 (2×), 115.6 (2×), 55.2, 42.6, 30.1, 28.7, 27.0 ppm. HRMS (ESI): calcd. for $C_{14}H_{14}NO_6^-$ $[M - H]^-$ 292.0821; found 292.0822.

**Diethyl (1*R**,2*S**,3*r**)-3-[(*tert*-Butoxycarbonyl)(4-nitrophenyl)-carbamoyl]cyclopropane-1,2-dicarboxylate (26):** To a solution of amide **24B** (5.0 mg, 0.014 mmol) in $CH_2Cl_2$ (0.2 mL) at 0 °C were added $Boc_2O$ (0.016 mL, 0.071 mmol), $Et_3N$ (0.010 mL, 0.071 mmol), and DMAP (0.2 mg, 0.007 mmol). After 1 h, the mixture was diluted with $CHCl_3$ (3 mL), and the resulting solution was washed with saturated aqueous $NH_4Cl$ (1 mL) and brine (1 mL), dried with $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0.8 g, EtOAc/hexane, 83:17) to give *N*-Boc imide **26** (6.2 mg, 97%) as a yellow oil; $R_f$ = 0.49 (EtOAc/hexane, 35:65). IR (film): $\tilde{\nu}$ = 2981, 1751, 1596, 1525, 1349, 1300, 1154 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.23 (d, $J$ = 9.2 Hz, 2 H), 7.41 (d, $J$ = 9.2 Hz, 2 H), 4.22–4.14 (m, 4 H), 3.10 (dd, $J$ = 9.6 Hz, 1 H), 2.46 (d, $J$ = 9.6 Hz, 2 H), 1.34 (s, 9 H), 1.25 (t, $J$ = 7.2 Hz, 6 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 168.3, 167.9 (2×), 151.5, 147.0, 144.5, 129.7 (2×), 124.2 (2×), 84.0, 61.4 (2×), 30.2, 27.7 (3×), 26.2 (2×), 14.1 (2×) ppm. HRMS (ESI): calcd. for $C_{21}H_{27}N_2O_9^+$ $[M + H]^+$ 451.1717; found 451.1727.

**Triethyl *trans*-Cyclopropane-1,2,3-tricarboxylate (5):** To a stirred solution of *N*-Boc imide **26** (3.6 mg, 0.0080 mmol) in EtOH (0.2 mL) at –10 °C was added $K_2CO_3$ (27.6 mg, 0.20 mmol). After stirring at room temp. for 5 h, the mixture was diluted with EtOAc (2 mL), and the resulting solution was washed with saturated aqueous $NH_4Cl$ (1 mL) and brine (1 mL), dried with $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0.5 g, EtOAc/hexane, 90:10) to give triethyl ester **5** (1.7 mg, 85%) as a colorless oil; $R_f$ = 0.58 (EtOAc/hexane, 30:70). IR (film): $\tilde{\nu}$ = 2984, 1733, 1447, 1369, 1338, 1183 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 4.14–4.07 (m, 6 H), 2.70 (dd, $J$ = 5.6, 5.6 Hz, 1 H), 2.47 (d, $J$ = 5.6 Hz, 2 H), 1.24–1.18 (m, 9 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 170.0, 167.5 (2×), 61.5, 61.4 (2×), 28.3 (2×), 25.5, 14.0 (3×) ppm. HRMS (ESI): calcd. for $C_{12}H_{19}O_6^+$ $[M + H]^+$ 259.1182; found 259.1184. The spectroscopic data for **5** were identical with those reported by Aggarwal et al.[20]

**(1*R**,2*R**,5*S**,6*R**)-*tert*-Butyl 2-Hydroxy-3-(4-nitrophenyl)-4-oxo-3-azabicyclo[3.1.0]hexane-6-carboxylate (27):** To a stirred solution of amido ester **23B** (5.0 mg, 0.014 mmol) in THF (0.200 mL) at –78 °C was added $LiAlH_4$ (0.001 mg, 0.03 mmol). After 3 h, MeOH (0.03 mL) and saturated aqueous potassium sodium tartrate (Rochelle salt, 0.02 mL) were slowly added, and the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (0.5 g, acetone/$CHCl_3$, 10:90) to give aminal **27** (2.0 mg, 43%) as a colorless oil; $R_f$ = 0.16 (acetone/$CHCl_3$, 10:90). IR (film): $\tilde{\nu}$ = 3344, 2917, 2844, 1722, 1594, 1516, 1340, 1150, 773 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.19 (d, $J$ = 8.8 Hz, 2 H), 7.85 (d, $J$ = 8.8 Hz, 2 H), 5.71 (s, 1 H), 3.04 (br., 1 H), 2.55 (dd, $J$ = 8.4, 5.8 Hz, 1 H), 2.34 (dd, $J$ = 8.2, 5.8 Hz, 1

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H), 2.27 (dd, $J$ = 8.4, 8.2 Hz, 1 H), 1.27 (s, 9 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 170.0, 166.3, 144.2, 143.0, 124.6 (2×), 121.2 (2×), 82.7, 82.6, 77.2, 27.8, 27.3 (3×), 26.3 ppm. HRMS (ESI): calcd. for $C_{16}H_{19}N_2O_6^+$ [M + H]$^+$ 335.1243; found 335.1249.

***tert*-Butyl (1*R**,2*R**,3*S**)-2-(Hydroxymethyl)-3-[(4-nitrophenyl)-carbamoyl]cyclopropanecarboxylate (28):** To a stirred solution of *N*-(4-nitrophenyl)imide **16** (3.4 mg, 0.010 mmol) in THF (0.200 mL) and MeOH (0.100 mL) at 0 °C was added $NaBH_4$ (0.0012 mg, 0.031 mmol). After 50 min, the mixture was diluted with $CHCl_3$ (2 mL), and the resulting solution was washed with saturated aqueous $NH_4Cl$ (1 mL), $H_2O$ (1 mL), and then brine (1 mL). The organic layer was dried with $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0.5 g, EtOAc/hexane, 70:30) to give alcohol **28** (2.6 mg, 76%) as a colorless oil; $R_f$ = 0.23 (EtOAc/hexane, 60:40). IR (film): $\tilde{\nu}$ = 3295, 2921, 2849, 1556, 1341, 1292, 1253, 1110, 1011, 886, 772 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.95 (br., 1 H), 8.19 (d, $J$ = 8.0 Hz, 2 H), 7.70 (d, $J$ = 8.0 Hz, 2 H), 4.11–4.06 (m, 2 H), 2.80 (br., 1 H), 2.27 (dd, $J$ = 9.2, 8.8 Hz, 1 H), 2.17 (dd, $J$ = 9.2, 8.8 Hz, 1 H), 1.92–1.88 (m, 1 H), 1.53 (s, 9 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 168.9, 166.5, 143.8, 143.4, 125.1 (2×), 119.0 (2×), 82.5, 57.9, 29.7, 28.0 (3×), 25.0, 24.9 ppm. HRMS (ESI): calcd. for $C_{16}H_{21}N_2O_6^+$ [M + H]$^+$ 337.1400; found 337.1404.

**Ethyl (1*S**,2*R**,3*S**)-2-(Hydroxymethyl)-3-[(4-nitrophenyl)carbamoyl]cyclopropanecarboxylate (29):** To a stirred solution of *N*-(4-nitrophenyl)imide **18** (730.0 mg, 2.38 mmol) in THF (23.8 mL) and MeOH (2.0 mL) at –10 °C was added $NaBH_4$ (270.4 mg, 7.15 mmol). After 10 min, the mixture was diluted with $CHCl_3$ (50 mL), and the resulting solution was washed with saturated aqueous $NH_4Cl$ (20 mL) and brine (15 mL), dried with $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (15 g, EtOAc/hexane, 50:50) to give alcohol **29** (695.6 mg, 95%) as a yellow oil; $R_f$ = 0.44 (EtOAc/hexane, 50:50). IR (film): $\tilde{\nu}$ = 3334, 3090, 2894, 1731, 1699, 1506, 1369, 1341, 1168 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.25 (s, 1 H), 8.07 (d, $J$ = 9.2 Hz, 2 H), 7.63 (d, $J$ = 9.2 Hz, 2 H), 4.16 (q, $J$ = 7.2 Hz, 2 H), 4.08 (dd, $J$ = 5.2, 4.4 Hz, 1 H), 3.83 (dd, $J$ = 9.2, 9.2 Hz, 1 H), 2.48 (dd, $J$ = 10.0, 5.2 Hz, 1 H), 2.38 (dd, $J$ = 10.0, 4.4 Hz, 1 H), 2.17 (m, 1 H), 1.26 (t, $J$ = 7.2 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ = 171.9, 168.0, 144.7, 143.0, 124.3 (2×), 118.8 (2×), 60.9, 57.6, 30.7, 28.4, 25.1, 13.1 ppm. HRMS (ESI): calcd. for $C_{14}H_{17}N_2O_6^+$ [M + H]$^+$ 309.1087; found 309.1075.

**Ethyl (1*S**,2*S**,3*R**)-2-[(4-Nitrophenyl)carbamoyl]-3-{[(triethylsilyl)oxy]methyl}cyclopropanecarboxylate (30):** To a stirred solution of alcohol **29** (1.26 g, 4.09 mmol) in $CH_2Cl_2$ (40.0 mL) at 0 °C were added TESCl (1.40 mL, 8.17 mmol), $Et_3N$ (1.13 mL, 8.17 mmol), and DMAP (49.8 mg, 0.41 mmol). After 20 min, the mixture was diluted with $CHCl_3$ (80 mL), and the resulting solution was washed with saturated aqueous $NH_4Cl$ (20 mL) and brine (20 mL), dried with $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (15 g, EtOAc/hexane, 70:30) to give TES ether **30** (1.43 g, 83%) as a colorless oil; $R_f$ = 0.53 (EtOAc/hexane, 50:50). IR (film): $\tilde{\nu}$ = 3334, 3090, 2894, 1731, 1699, 1506, 1369, 1341, 1168 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.46 (s, 1 H), 8.17 (d, $J$ = 9.2 Hz, 2 H), 7.67 (d, $J$ = 9.2 Hz, 2 H), 4.16 (q, $J$ = 7.2 Hz, 2 H), 4.04 (dd, $J$ = 11.2, 5.6 Hz, 1 H), 3.67 (dd, $J$ = 11.2, 9.2 Hz, 1 H), 2.38 (d, $J$ = 7.6 Hz, 2 H), 2.15 (m, 1 H), 1.26 (t, $J$ = 7.2 Hz, 3 H), 0.86 (t, $J$ = 8.0 Hz, 9 H), 0.54 (q, $J$ = 8.0 Hz, 6 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 172.4, 166.9, 143.9, 143.3, 125.0 (2×), 118.8 (2×), 61.6, 59.1, 31.3, 29.5, 25.1, 14.1, 6.6 (3×), 4.1 (3×) ppm. HRMS (ESI): calcd. for $C_{20}H_{31}N_2O_6Si^+$ [M + H]$^+$ 423.1951; found 423.1942.

**Ethyl (1*S**,2*S**,3*R**)-2-[(*tert*-Butoxycarbonyl)(4-nitrophenyl)-carbamoyl]-3-{[(triethylsilyl)oxy]methyl}cyclopropanecarboxylate (31):** To a stirred solution of amide **30** (277.5 mg, 0.660 mmol) in $CH_2Cl_2$ (6.6 mL) at 0 °C were added $Boc_2O$ (0.300 mL, 1.31 mmol), $Et_3N$ (0.182 mL, 1.31 mmol), and DMAP (40.1 mg, 0.33 mmol). After stirring at room temp. for 30 min, the mixture was diluted with $CHCl_3$ (20 mL), and the resulting solution was washed with saturated aqueous $NH_4Cl$ (5 mL) and brine (5 mL), dried with $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10 g, EtOAc/hexane, 20:80) to give *N*-Boc imide **31** (294.1 mg, 86%) as a yellow oil; $R_f$ = 0.55 (EtOAc/hexane, 20:80). IR (film): $\tilde{\nu}$ = 2956, 2876, 1744, 1693, 1526, 1458, 1369, 1347, 1256, 1153 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.24 (d, $J$ = 8.8 Hz, 2 H), 7.31 (d, $J$ = 8.8 Hz, 2 H), 4.13 (q, $J$ = 7.2 Hz, 2 H), 3.92 (dd, $J$ = 11.2, 6.0 Hz, 1 H), 3.54 (dd, $J$ = 11.2, 9.2 Hz, 1 H), 3.32 (dd, $J$ = 10.4, 4.8 Hz, 1 H), 2.42 (dd, $J$ = 6.0, 4.8 Hz, 1 H), 2.22 (m, 1 H), 1.41 (s, 9 H), 1.25 (t, $J$ = 7.2 Hz, 3 H), 0.94 (t, $J$ = 8.0 Hz, 9 H), 0.59 (q, $J$ = 8.0 Hz, 6 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.4, 170.5, 151.3, 147.0, 144.7, 129.4 (2×), 124.3 (2×), 84.6, 61.1, 59.0, 32.3, 29.6, 27.7 (3×), 26.5, 14.1, 6.7 (3×), 4.3 (3×) ppm. HRMS (ESI): calcd. for $C_{25}H_{39}N_2O_8Si^+$ [M + H]$^+$ 523.2476; found 523.2473.

**Diethyl (1*S**,2*S**)-3-(Hydroxymethyl)cyclopropane-1,2-dicarboxylate (32):** To a stirred solution of *N*-Boc imide **31** (1.79 g, 3.42 mmol) in EtOH (100 mL) at room temp. was added $K_2CO_3$ (13.8 g, 100 mmol). After 20 min, the mixture was filtered through a pad of silica gel (20 g, $CHCl_3$), and the filtrate was concentrated under reduced pressure to give the crude siloxy diester (1.72 g) as a yellow oil, which was used without purification in the next reaction. To a stirred solution of the crude siloxy diester (1.72 g) in THF (34.2 mL) at room temp. were added AcOH (0.800 mL, 14.7 mmol) and TBAF (1.0 M in THF, 10.26 mL, 10.26 mmol). After 1 h, the mixture was diluted with $CHCl_3$ (100 mL), and the resulting solution was washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL), dried with $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (20 g, EtOAc/hexane, 40:60) to give alcohol **32** (546.7 mg, 74% for 2 steps from **31**) as a colorless oil; $R_f$ = 0.36 (EtOAc/hexane, 30:70). IR (film): $\tilde{\nu}$ = 3441, 2982, 1723, 1372, 1179 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.12 (m, 4 H), 3.91 (dd, $J$ = 12.0, 5.2 Hz, 1 H), 3.77 (dd, $J$ = 12.0, 7.6 Hz, 1 H), 2.29 (d, $J$ = 7.6 Hz, 2 H), 1.84 (m, 1 H), 1.22 (t, $J$ = 7.2 Hz, 6 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 169.3 (2×), 61.3 (2×), 57.5, 25.1, 24.2 (2×), 14.1 (2×) ppm. HRMS (ESI): calcd. for $C_{10}H_{17}O_5^+$ [M + H]$^+$ 217.1076; found 217.1077.

**Diethyl (1*R**,2*R**)-3-(Bromomethyl)cyclopropane-1,2-dicarboxylate (33):** To a stirred solution of alcohol **32** (10.2 mg, 0.047 mmol) in $CH_2Cl_2$ (2.1 mL) at room temp. were added $PPh_3$ (24.7 mg, 0.094 mmol) and $CBr_4$ (46.9 mg, 0.14 mmol). After 1 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (2 g, EtOAc/hexane, 30:70) to give bromide **33** (11.2 mg, 85%) as a colorless oil; $R_f$ = 0.49 (EtOAc/hexane, 15:85). IR (film): $\tilde{\nu}$ = 2981, 1722, 1314, 1205, 1153 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.21–4.11 (m, 4 H), 3.73 (m, 1 H), 3.55 (m, 1 H), 2.44 (dd, $J$ = 8.4, 5.6 Hz, 1 H), 2.33–2.28 (m, 2 H), 1.30–1.23 (m, 6 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 170.4, 169.2, 61.5, 61.4, 30.4, 30.0, 28.6, 28.5, 14.2, 14.1 ppm. HRMS (ESI): calcd. for $C_{10}H_{16}O_4Br^+$ [M + H]$^+$ 279.0232; found 279.0238.

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**Diethyl (1*S**,2*S**)-3-[(Dimethylamino)methyl]cyclopropane-1,2-dicarboxylate (34):** A solution of bromide **33** (22.4 mg, 0.080 mmol) and dimethylamine (2.0 M in THF, 0.400 mL, 0.80 mmol) in toluene (0.4 mL) was heated to 125 °C in a sealed tube. After 3 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1 g, MeOH/$CHCl_3$, 10:90) to give tertiary amine **34** (19.5 mg, 100%) as a yellow oil; $R_f$ = 0.58 (MeOH/$CHCl_3$, 50:50). IR (film): $\tilde{\nu}$ = 3439, 2981, 1722, 1370, 1203, 1176 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 4.16–4.09 (m, 4 H), 2.89–2.81 (m, 2 H), 2.42 (s, 6 H), 2.36 (dd, *J* = 9.2, 5.2 Hz, 1 H), 2.16 (dd, *J* = 5.2, 5.2 Hz 1 H), 2.09–2.05 (m, 1 H) 1.26–1.21 (m, 6 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 170.5, 169.9, 61.4 (2×), 54.5, 44.0 (2×), 26.9, 26.3, 24.9, 14.1, 14.1 ppm. HRMS (ESI): calcd. for $C_{12}H_{22}NO_4^+$ $[M + H]^+$ 244.1549; found 244.1543.

**1-[(2*S**,3*S**)-2,3-Bis(ethoxycarbonyl)cyclopropyl]-*N*,*N*,*N*-trimethylmethanaminium Iodide (35):** A suspension of tertiary amine **34** (9.8 mg, 0.040 mmol), MeI (0.150 mL, 3.62 mmol), and $NaHCO_3$ (10.1 mg, 0.121 mmol) in toluene (0.15 mL) was heated to 125 °C in a sealed tube. After 7 h, the mixture was concentrated under reduced pressure. To the residue was added $CHCl_3$ (2 mL), and the insoluble materials were removed by filtration. The filtrate was concentrated under reduced pressure to give the crude quaternary ammonium iodide **35** (14.5 mg) as a brown solid, which was used without purification in the next reaction; $R_f$ = 0.75 (BuOH/AcOH/$H_2O$, 33:33:33). IR (KBr): $\tilde{\nu}$ = 3441, 2981, 1716, 1305, 1222, 1185 $cm^{-1}$. $^1H$ NMR (400 MHz, $D_2O$): $\delta$ = 4.26–4.10 (m, 4 H), 4.01 (dd, *J* = 13.6, 6.4 Hz, 1 H), 3.89 (dd, *J* = 13.6, 8.0 Hz, 1 H), 3.48 (s, 9 H), 2.55 (dd, *J* = 8.8, 5.2 Hz, 1 H), 2.31 (dd, *J* = 5.2, 5.2 Hz, 1 H), 2.15 (m, 1 H), 1.29 (t, *J* = 7.2 Hz, 6 H) ppm. $^{13}C$ NMR (100 MHz, $D_2O$): $\delta$ = 169.6, 169.2, 62.5, 62.4 (2×), 54.1 (3×), 26.8, 25.9, 20.8, 14.2 (2×) ppm. HRMS (ESI): calcd. for $C_{13}H_{24}NO_4^+$ $[M - I]^+$ 258.1705; found 258.1690.

**(±)-Dysibetaine CPa (1):** A suspension of crude quaternary ammonium iodide **35** (3.2 mg, 0.01 mmol), in hydrochloric acid (6 M solution, 1.0 mL) was heated to 90 °C with stirring. After 6 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on reversed-phase silica gel (1 g, MeOH/$H_2O$, 10:90) to give dysibetaine CPa (**1**, 1.3 mg, 74% for 2 steps from **34**) as a yellow solid; $R_f$ = 0.28 (BuOH/AcOH/$H_2O$, 33:33:33). IR (KBr): $\tilde{\nu}$ = 3410, 3013, 2609, 1733, 1472, 1233, 1184 $cm^{-1}$. $^1H$ NMR (400 MHz, $D_2O$): $\delta$ = 3.68–3.57 (m, 2 H, 1-$H_2$), 3.10 [s, 9 H, 1-N($CH_3$)$_3$], 2.44 (dd, *J* = 9.2, 5.2 Hz, 1 H, 3-H or 4-H), 2.26 (dd, *J* = 5.2, 5.2 Hz, 1 H, 3-H or 4-H), 2.17 (m, 1 H, 2-H) ppm. $^{13}C$ NMR (100 MHz, $D_2O$): $\delta$ = 175.0 (C-5 or C-6), 174.0 (C-5 or C-6), 63.7 (C-1), 53.9 [3×, 1-N($CH_3$)$_3$], 27.8 (C-3 or C-4), 27.7 (C-3 or C-4), 22.0 (C-2) ppm. HRMS (ESI): calcd. for $C_9H_{16}NO_4^+$ $[M + H]^+$ 202.1079; found 202.1072. The chromatographic data as well as the $^1H$ and $^{13}C$ NMR spectroscopic data were identical with those for the natural product reported by Sakai et al.[5]

**Ethyl (1*R**,2*R**,3*S**)-2-(Hydroxymethyl)-3-[(4-nitrophenyl)carbamoyl]cyclopropanecarboxylate (36) and Ethyl (1*R**,2*R**,5*S**,6*R**)-2-Hydroxy-3-(4-nitrophenyl)-4-oxo-3-azabicyclo[3.1.0]hexane-6-carboxylate (37):** To a stirred solution of 3-*epi*-imide **17** (124.6 mg, 0.410 mmol) in THF (4.0 mL) and MeOH (2.0 mL) at –10 °C was added $NaBH_4$ (46.4 mg, 1.23 mmol). After 2 h, the mixture was diluted with $CHCl_3$ (10 mL), and the resulting solution was washed with saturated aqueous $NH_4Cl$ (3 mL) and brine (3 mL), dried with $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (5 g, EtOAc/hexane, 80:20) to give 3-*epi*-alcohol **36** (70.4 mg, 55%) and 3-*epi*-aminal **37** (41.6 mg, 33%) as yellow oils. Data for 3-*epi*-alcohol **36**: $R_f$ = 0.21 (EtOAc/hexane, 60:40). IR (film): $\tilde{\nu}$ = 3518, 3265, 2926, 1716, 1653, 1507, 1378, 1341, 1174 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 9.07 (br. s, 1 H), 8.18 (d, *J* = 9.2 Hz, 2 H), 7.70 (d, *J* = 9.2 Hz, 2 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 4.14–4.04 (m, 2 H), 2.35 (dd, *J* = 8.8, 8.8 Hz, 1 H), 2.24 (dd, *J* = 8.8, 8.8 Hz, 1 H), 1.94 (m, 1 H), 1.23 (t, *J* = 7.2 Hz, 3 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 169.8, 166.3, 143.7, 143.5, 125.1 (2×), 119.2 (2×), 61.6, 57.7, 28.2, 25.1, 23.6, 14.1 ppm. HRMS (ESI): calcd. for $C_{14}H_{17}N_2O_6^+$ $[M + H]^+$ 309.1087; found 309.1081. Data for 3-*epi*-aminal **37**: $R_f$ = 0.34 (EtOAc/hexane, 60:40). IR (film): $\tilde{\nu}$ = 3372, 2983, 1732, 1653, 1519, 1382, 1341, 1191 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.12 (d, *J* = 9.2 Hz, 2 H), 7.79 (d, *J* = 9.2 Hz, 2 H), 5.59 (d, *J* = 1.6 Hz, 1 H), 4.13 (br. s, 1 H), 3.99 (q, *J* = 7.2 Hz, 2 H), 2.51 (ddd, *J* = 8.4, 6.0, 1.6 Hz, 1 H), 2.38 (dd, *J* = 8.4, 6.0 Hz, 1 H), 2.26 (dd, *J* = 8.4, 8.4 Hz, 1 H), 1.10 (t, *J* = 7.2 Hz, 3 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 170.3, 167.6, 144.3, 143.0, 124.5 (2×), 121.3 (2×), 83.0, 61.7, 27.0, 26.8, 26.1, 14.0 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}N_2O_6^+$ $[M + H]^+$ 307.0930; found 307.0932.

**Ethyl (1*R**,2*S**,3*R**)-2-[(4-Nitrophenyl)carbamoyl]-3-{[(triethylsilyl)oxy]methyl}cyclopropanecarboxylate (38):** To a stirred solution of 3-*epi*-alcohol **36** (10.0 mg, 0.032 mmol) in $CH_2Cl_2$ (0.200 mL) at 0 °C were added 2,6-lutidine (0.016 mL, 0.14 mmol) and TESOTf (0.015 mL, 0.064 mmol). After 20 min, $Et_3N$ (0.030 mL) was added at 0 °C, and the mixture was diluted with $CHCl_3$ (5 mL). The resulting solution was washed with saturated aqueous $NH_4Cl$ (2 mL) and brine (2 mL), dried with $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (4 g, EtOAc/hexane, 40:60) to give 3-*epi*-TES ether **38** (10.7 mg, 84%) as a yellow oil; $R_f$ = 0.79 (EtOAc/hexane, 60:40). IR (film): $\tilde{\nu}$ = 3308, 2955, 1733, 1649, 1507, 1410, 1378, 1341, 1260, 1162 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 9.91 (s, 1 H), 8.10 (d, *J* = 9.2 Hz, 2 H), 7.65 (d, *J* = 9.2 Hz, 2 H), 4.22–4.01 (m, 2 H), 4.09 (q, *J* = 7.2 Hz, 2 H), 2.35 (dd, *J* = 9.2, 9.2 Hz, 1 H), 2.15 (dd, *J* = 9.2, 9.2 Hz, 1 H), 1.80 (m, 1 H), 1.16 (t, *J* = 7.2 Hz, 3 H), 0.92 (t, *J* = 8.0 Hz, 9 H), 0.61 (q, *J* = 8.0 Hz, 6 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 169.7, 166.0, 144.2, 143.0, 124.8 (2×), 118.9 (2×), 61.1, 57.7, 28.6, 25.5, 22.8, 13.9, 6.5 (3×), 4.3 (3×) ppm. HRMS (ESI): calcd. for $C_{20}H_{31}N_2O_6Si^+$ $[M + H]^+$ 423.1951; found 423.1945.

**Ethyl (1*R**,2*S**,3*R**)-2-[(*tert*-Butoxycarbonyl)(4-nitrophenyl)carbamoyl]-3-{[(triethylsilyl)oxy]methyl}cyclopropanecarboxylate (39):** To a stirred solution of 3-*epi*-amide **38** (150.0 mg, 0.354 mmol) in $CH_2Cl_2$ (10.0 mL) at 0 °C were added $Boc_2O$ (0.162 mL, 0.71 mmol), $Et_3N$ (0.098 mL, 0.71 mmol), and DMAP (21.6 mg, 0.177 mmol). After stirring at room temp. for 50 min, the mixture was diluted with $CHCl_3$ (15 mL), and the resulting solution was washed with saturated aqueous $NH_4Cl$ (7 mL) and brine (7 mL), dried with $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (10 g, EtOAc/hexane, 80:20) to give 3-*epi*-*N*-Boc imide **39** (180.7 mg, 97%) as a yellow oil; $R_f$ = 0.75 (EtOAc/hexane, 30:70). IR (film): $\tilde{\nu}$ = 2956, 2876, 1747, 1699, 1526, 1457, 1347, 1325, 1265, 1183 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.24 (d, *J* = 8.8 Hz, 2 H), 7.36 (d, *J* = 8.8 Hz, 2 H), 4.18–4.11 (m, 3 H), 3.86 (dd, *J* = 11.6, 9.2 Hz, 1 H), 2.86 (dd, *J* = 8.8, 8.8 Hz, 1 H), 2.33 (dd, *J* = 8.8, 8.8 Hz, 1 H), 1.97 (m, 1 H), 1.35 (s, 9 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 0.91 (t, *J* = 8.0 Hz, 9 H), 0.55 (q, *J* = 8.0 Hz, 6 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 170.0, 169.7, 151.3, 147.0, 144.7, 129.6 (2×), 124.2 (2×), 84.0, 60.8, 57.8, 29.0, 28.5, 27.7 (3×), 25.0, 14.2, 6.7 (3×), 4.3 (3×) ppm. HRMS (ESI): calcd. for $C_{25}H_{39}N_2O_8Si^+$ $[M + H]^+$ 523.2476; found 523.2478.

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**Diethyl (1*R*,2*S*,3*r*)-3-(Hydroxymethyl)cyclopropane-1,2-dicarboxylate (40):** To a stirred solution of 3-*epi*-*N*-Boc imide **39** (26.4 mg, 0.050 mmol) in EtOH (3.0 mL) at room temp. was added $K_2CO_3$ (415.0 mg, 3.00 mmol). After 2 h, the mixture was filtered through a pad of silica gel (10 g, $CHCl_3$), and the filtrate was concentrated under reduced pressure to give the crude siloxy diester (30.9 mg) as a yellow oil, which was used without purification in the next reaction. To a stirred solution of the crude siloxy diester (30.9 mg) in THF (0.900 mL) at room temp. were added AcOH (0.020 mL, 0.37 mmol) and TBAF (1.0 M in THF, 0.28 mL, 0.28 mmol). After 3 h, the mixture was diluted with $CHCl_3$ (10 mL), and the resulting solution was washed with saturated aqueous $NaHCO_3$ (4 mL) and brine (4 mL), dried with $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (3 g, EtOAc/hexane, 40:60) to give 3-*epi*-alcohol **40** (9.1 mg, 83% for 2 steps from **39**) as a colorless oil; $R_f$ = 0.12 (EtOAc/hexane, 30:70). IR (film): $\tilde{\nu}$ = 3341, 2983, 1732, 1378, 1179 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 4.17–4.12 (m, 4 H), 3.94 (d, $J$ = 8.0 Hz, 2 H), 2.15 (d, $J$ = 8.0 Hz, 2 H), 1.84 (m, 1 H), 1.22 (t, $J$ = 7.2 Hz, 6 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 169.3 (2×), 61.3 (2×), 57.5, 25.1, 24.2 (2×), 14.1 (2×) ppm. HRMS (ESI): calcd. for $C_{10}H_{17}O_5^+$ $[M + H]^+$ 217.1076; found 217.1069.

**Diethyl (1*R*,2*S*,3*s*)-3-(Bromomethyl)cyclopropane-1,2-dicarboxylate (41):** To a stirred solution of 3-*epi*-alcohol **40** (27.7 mg, 0.146 mmol) in $CH_2Cl_2$ (2.1 mL) at room temp. were added $PPh_3$ (100.8 mg, 0.384 mmol) and $CBr_4$ (169.9 mg, 0.512 mmol). After 1 h, the mixture was diluted with $CHCl_3$ (10 mL), and the resulting solution was washed with saturated aqueous $NaHCO_3$ (3 mL) and brine (3 mL), dried with $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (2 g, EtOAc/hexane, 40:60) to give 3-*epi*-bromide **41** (13.1 mg, 38%) as a colorless oil; $R_f$ = 0.61 (EtOAc/hexane = 30:70). IR (film): $\tilde{\nu}$ = 2982, 1738, 1378, 1203, 1158 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 4.17 (q, $J$ = 7.2 Hz, 2 H), 4.16 (q, $J$ = 7.2 Hz, 2 H), 3.95 (d, $J$ = 7.6 Hz, 2 H), 2.25 (d, $J$ = 8.8 Hz, 2 H), 2.01 (m, 1 H), 1.25 (t, $J$ = 7.2 Hz, 6 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 168.0 (2×), 61.2 (2×), 28.4, 26.6 (2×), 26.4, 14.1 (2×) ppm. HRMS (ESI): calcd. for $C_{10}H_{16}O_4Br^+$ $[M + H]^+$ 279.0232; found 279.0243.

**(1*R*,2*S*,3*r*)-Diethyl 3-[(Dimethylamino)methyl]cyclopropane-1,2-dicarboxylate (42):** A solution of 3-*epi*-bromide **41** (3.5 mg, 0.013 mmol) and dimethylamine (2.0 M in THF, 0.050 mL, 0.10 mmol) in toluene (0.1 mL) was heated to 125 °C in a sealed tube. After 9.5 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1 g, MeOH/$CHCl_3$, 17:83) to give 3-*epi*-tertiary amine **42** (2.5 mg, 83%) as a yellow oil; $R_f$ = 0.35 (MeOH/$CHCl_3$, 50:50). IR (film): $\tilde{\nu}$ = 3431, 2982, 1732, 1379, 1208, 1178 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 4.18–4.09 (m, 4 H), 3.73 (d, $J$ = 6.0 Hz, 2 H), 2.84 (s, 6 H), 2.41 (m, 1 H), 2.32 (d, $J$ = 9.6 Hz, 2 H), 1.25 (t, $J$ = 7.2 Hz, 6 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 168.2 (2×), 61.2 (2×), 52.3, 42.7 (2×), 23.7 (2×), 18.6, 14.1 (2×) ppm. HRMS (ESI): calcd. for $C_{12}H_{22}NO_4^+$ $[M + H]^+$ 244.1549; found 244.1542.

**1-[(1*r*,2*R*,3*S*)-2,3-Bis(ethoxycarbonyl)cyclopropyl]-*N*,*N*,*N*-trimethylmethanaminium Iodide (43):** A suspension of 3-*epi*-tertiary amine **42** (2.8 mg, 0.012 mmol), MeI (0.100 mL, 2.41 mmol), and $NaHCO_3$ (2.0 mg, 0.036 mmol) in toluene (0.100 mL) was heated to 125 °C in a sealed tube. After 6 h, the mixture was concentrated under reduced pressure. To the residue was added $CHCl_3$ (1 mL), and the insoluble materials were removed by filtration. The filtrate was concentrated under reduced pressure to give the crude 3-*epi*-quaternary ammonium iodide **43** (4.3 mg) as a brown solid, which was used without purification in the next reaction; $R_f$ = 0.42 (MeOH/$CHCl_3$, 30:70). IR (KBr): $\tilde{\nu}$ = 3421, 2976, 1733, 1378, 1207, 1182 $cm^{-1}$. $^1H$ NMR (400 MHz, $D_2O$): $\delta$ = 4.16–4.06 (m, 4 H), 3.86 (d, $J$ = 6.8 Hz, 2 H), 3.10 (s, 9 H), 2.55 (d, $J$ = 8.8 Hz, 2 H), 2.05 (m, 1 H), 1.17 (t, $J$ = 7.2 Hz, 6 H) ppm. $^{13}C$ NMR (100 MHz, $D_2O$): $\delta$ = 170.2 (2×), 62.7 (2×), 53.0, 48.8 (3×), 23.9 (2×), 17.2, 13.2 (2×) ppm. HRMS (ESI): calcd. for $C_{13}H_{24}NO_4^+$ $[M - I]^+$ 258.1705; found 258.1699.

***meso*-3-*epi*-Dysibetaine CPa (44):** A suspension of the crude 3-*epi*-quaternary ammonium iodide **43** (4.3 mg) in hydrochloric acid (6 M solution, 1.0 mL) was heated to 90 °C with stirring. After 8.5 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on reversed-phase silica gel (1 g, MeOH/$H_2O$, 10:90) to give DBCPa diastereomer **44** (1.7 mg, 74% for 2 steps from **42**) as a yellow solid; $R_f$ = 0.34 (BuOH/AcOH/$H_2O$, 33:33:33). IR (KBr): $\tilde{\nu}$ = 3436, 2918, 1733, 1559, 1436, 1212, 1189 $cm^{-1}$. $^1H$ NMR (400 MHz, $D_2O$): $\delta$ = 3.84 (d, $J$ = 6.8 Hz, 2 H, 1-$H_2$), 3.09 [s, 9 H, 1-N($CH_3$)$_3$], 2.43 (d, $J$ = 8.8 Hz, 2 H, 3-H and 4-H), 2.01 (m, 1 H, 2-H) ppm. $^{13}C$ NMR (100 MHz, $D_2O$): $\delta$ = 172.8 (2×, C-5 and C-6), 61.4 (C-1), 52.9 [3×, 1-N-($CH_3$)$_3$], 24.6 (2×, C-3 and C-4), 17.2 (C-2) ppm. HRMS (ESI): calcd. for $C_9H_{16}NO_4^+$ $[M + H]^+$ 202.1079; found 202.1086.

**(1*S**,2*S**,3*S**)-2-Carboxy-3-[(dimethylammonio)methyl]cyclopropanecarboxylate [(±)-Dysibetaine CPa Tertiary Ammonium Analog 45]:** A suspension of amino diester **34** (9.8 mg, 0.040 mmol) in hydrochloric acid (6 M solution, 1.0 mL) was heated to 90 °C with stirring. After 4.5 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on reversed-phase silica gel (1 g, MeOH/$H_2O$, 10:90) to give DBCPa tertiary ammonium analog **45** (6.6 mg, 88%) as a yellow solid; $R_f$ = 0.43 (BuOH/AcOH/$H_2O$, 33:33:33). IR (KBr): $\tilde{\nu}$ = 3404, 2966, 2739, 1717, 1464, 1195 $cm^{-1}$. $^1H$ NMR (400 MHz, $D_2O$): $\delta$ = 3.49–3.39 (m, 2 H, 1-$H_2$), 2.86 [s, 3 H, 1-N($CH_3$)], 2.83 [s, 3 H, 1-N($CH_3$)], 2.42 (dd, $J$ = 9.2, 5.2 Hz, 1 H, 3-H or 4-H), 2.28 (dd, $J$ = 5.2, 5.2 Hz, 1 H, 3-H or 4-H), 2.10 (m, 1 H, 2-H) ppm. $^{13}C$ NMR (100 MHz, $D_2O$): $\delta$ = 173.9 (C-5 or C-6), 172.9 (C-5 or C-6), 54.2 (C-1), 42.7 [1-N($CH_3$)], 42.6 [1-N($CH_3$)], 26.9 (C-3 or C-4), 26.3 (C-3 or C-4), 22.3 (C-2) ppm. HRMS (ESI): calcd. for $C_8H_{14}NO_4^+$ $[M + H]^+$ 188.0923; found 188.0912.

**(1*R*,2*S*,3*S*)-2-Carboxy-3-[(dimethylammonio)methyl]cyclopropanecarboxylate (*meso*-3-*epi*-Dysibetaine CPa Tertiary Ammonium Analog 46):** A suspension of 3-*epi*-amino diester **42** (7.6 mg, 0.031 mmol) in hydrochloric acid (6 M solution, 1.0 mL) was heated to 90 °C with stirring. After 4.5 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on reversed-phase silica gel (1 g, MeOH/$H_2O$, 10:90) to give 3-*epi*-DBCPa tertiary ammonium analog **46** (2.5 mg, 100%) as a yellow solid; $R_f$ = 0.35 (MeOH/$CHCl_3$, 50:50). IR (KBr): $\tilde{\nu}$ = 2924, 2754, 1734, 1437, 1180 $cm^{-1}$. $^1H$ NMR (400 MHz, $D_2O$): $\delta$ = 3.51 (d, $J$ = 8.0 Hz, 2 H, 1-$H_2$), 2.83 [s, 6 H, 1-N-($CH_3$)$_2$], 2.31 (d, $J$ = 8.4 Hz, 2 H, 3-H and 4-H), 1.87 (m, 1 H, 2-H) ppm. $^{13}C$ NMR (100 MHz, $D_2O$): $\delta$ = 173.6 [2×, C-5 and C-6], 53.2 (C-1), 42.5 [2×, 1-N($CH_3$)$_2$], 25.1 (2×, C-3 and C-4), 17.9 (C-2) ppm. HRMS (ESI): calcd. for $C_8H_{14}NO_4^+$ $[M + H]^+$ 188.0923; found 188.0915.

**(1*S**,2*S**)-Diethyl 3-(Azidomethyl)cyclopropane-1,2-dicarboxylate (47):** To a stirred solution of bromide **33** (26.7 mg, 0.096 mmol) in DMF (0.500 mL) at room temp. were added $Bu_4NI$ (88.0 mg, 0.239 mmol) and $NaN_3$ (31.0 mg, 0.478 mmol). After stirring at 80 °C for 2.5 h, the mixture was cooled to room temp. and then poured into $H_2O$ (5 mL). The mixture was extracted with EtOAc

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(4 × 5 mL), and the combined organic extracts were washed with brine (3 mL) and dried with $Na_2SO_4$. Concentration under reduced pressure gave a residue, which was purified by column chromatography on silica gel (2.5 g, EtOAc/hexane, 20:80) to give azide **47** (16.9 mg, 73%) as a colorless oil; $R_f$ = 0.62 (EtOAc/hexane = 20:80). IR (film): $\tilde{\nu}$ = 2983, 2097, 1722, 1456, 1369, 1178 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 4.19–4.11 (m, 4 H), 3.59 (dd, $J$ = 13.2, 6.4 Hz, 1 H), 3.50 (dd, $J$ = 13.2, 9.0 Hz, 1 H), 2.37 (dd, $J$ = 9.2, 4.8 Hz, 1 H), 2.24 (dd, $J$ = 5.6, 4.8 Hz, 1 H), 2.08 (dddd, $J$ = 9.2, 9.0, 6.4, 5.6 Hz, 1 H), 1.29–1.24 (m, 6 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 170.6, 169.8, 61.6, 61.4, 47.6, 27.1, 26.7, 26.0, 14.1 (2×) ppm. HRMS (ESI): calcd. for $C_{10}H_{15}N_3O_4Na^+$ [M + Na]$^+$ 264.0960; found 264.0962.

**Diethyl (1*R*,2*S*,3*r*)-3-(Azidomethyl)cyclopropane-1,2-dicarboxylate (48):** To a stirred solution of 3-*epi*-bromide **41** (10.0 mg, 0.036 mmol) in DMF (0.200 mL) at room temp. were added $Bu_4NI$ (33.0 mg, 0.090 mmol) and $NaN_3$ (11.6 mg, 0.179 mmol). After stirring at 80 °C for 6.5 h, the mixture was cooled to room temp. and then poured into $H_2O$ (0.2 mL). The mixture was extracted with EtOAc (3 × 1 mL), and the combined organic extracts were washed with brine (2 mL) and dried with $Na_2SO_4$. Concentration under reduced pressure gave a residue, which was purified by column chromatography on silica gel (0.3 g, EtOAc/hexane, 10:90) to give 3-*epi*-azide **48** (6.5 mg, 75%) as a colorless oil; $R_f$ = 0.47 (EtOAc/hexane, 20:80). IR (film): $\tilde{\nu}$ = 2983, 2097, 1733, 1381, 1351, 1199, 1028 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 4.19–4.13 (m, 4 H), 3.84 (d, $J$ = 7.6 Hz, 2 H), 2.21 (d, $J$ = 9.0 Hz, 2 H), 1.75 (m, 1 H), 1.27–1.23 (m, 6 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 168.3 (2×), 61.2 (2×), 46.2, 23.8 (2×), 23.0, 14.1 (2×) ppm. HRMS (ESI): calcd. for $C_{10}H_{15}N_3O_4Na^+$ [M + Na]$^+$ 264.0960; found 264.0970.

**Diethyl (1*S**,2*S**)-3-{[(*tert*-Butoxycarbonyl)amino]methyl}-cyclopropane-1,2-dicarboxylate (49):** To a solution of azide **47** (16.9 mg, 0.070 mmol) in THF (0.175 mL) and MeOH (0.525 mL) at room temp. were added $Boc_2O$ (0.077 mg, 0.35 mmol) and $Pd(OH)_2$ (3.0 mg). After stirring under a hydrogen atmosphere for 4 h, the mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (2.5 g, EtOAc/hexane, 30:70) to give *N*-Boc amine **49** (16.9 mg, 76%) as a colorless oil; $R_f$ = 0.42 (EtOAc/hexane, 30:70). IR (film): $\tilde{\nu}$ = 2980, 1739, 1723, 1520, 1368, 1252, 1180 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 4.67 (br., 1 H), 4.18–4.10 (m, 4 H), 3.50 (m, 1 H), 3.28 (m, 1 H), 2.28 (dd, $J$ = 9.6, 4.8 Hz, 1 H), 2.19 (dd, $J$ = 4.8, 4.8 Hz, 1 H), 2.06 (m, 1 H), 1.42 (s, 9 H), 1.28–1.22 (m, 6 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 171.1, 170.1, 155.7, 61.3 (2×), 37.5, 28.6, 28.4 (4×), 26.8, 26.4, 14.2 (2×) ppm. HRMS (ESI): calcd. for $C_{15}H_{25}NO_6Na^+$ [M + Na]$^+$ 338.1580; found 338.1583.

**(1*R*,2*S*,3*r*)-Diethyl 3-{[(*tert*-Butoxycarbonyl)amino]methyl}-cyclopropane-1,2-dicarboxylate (50):** To a solution of 3-*epi*-azide **48** (10.0 mg, 0.042 mmol) in THF (0.100 mL) and MeOH (0.300 mL) at room temp. were added $Boc_2O$ (0.045 mg, 0.21 mmol) and $Pd(OH)_2$ (2.0 mg). After stirring under a hydrogen atmosphere for 3 h, the mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1.8 g, EtOAc/hexane, 40:60) to give 3-*epi*-*N*-Boc amine **50** (7.3 mg, 56%) as a colorless oil; $R_f$ = 0.42 (EtOAc/hexane, 30:70). IR (film): $\tilde{\nu}$ = 2979, 1731, 1717, 1505, 1379, 1176 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 5.21 (br., 1 H), 4.15–4.11 (m, 4 H), 3.56 (dd, $J$ = 7.6, 6.8 Hz, 2 H), 2.10 (d, $J$ = 8.6 Hz, 2 H), 1.80 (m, 1 H), 1.42 (s, 9 H), 1.26–1.23 (m, 6 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 168.8, 156.0, 79.0, 60.9 (2×), 35.3, 28.3 (4×), 23.8 (2×), 23.3, 14.0 (2×) ppm. HRMS (ESI): calcd. for $C_{15}H_{25}NO_6Na^+$ [M + Na]$^+$ 338.1580; found 338.1567.

**(1*S**,2*S**,3*S**)-2-(Ammoniomethyl)-3-carboxycyclopropanecarboxylate [(±)-*N*-Desmethyldysibetaine CPa, 51]:** A suspension of *N*-Boc-amino diester **49** (2.7 mg, 0.0086 mmol) in hydrochloric acid (6 M solution, 0.200 mL) was heated to 90 °C with stirring. After 7.5 h, the mixture was concentrated, and the residue was purified by column chromatography on reversed-phase silica gel (1 g, MeOH/$H_2O$, 10:90) to give DBCPa *N*-desmethyl analog **51** (1.3 mg, 100%) as a yellow solid; $R_f$ = 0.60 (BuOH/AcOH/$H_2O$, 33:33:33). IR (KBr): $\tilde{\nu}$ = 3419, 3039, 1719, 1645, 1399, 1221, 974 $cm^{-1}$. $^1H$ NMR (400 MHz, $D_2O$): $\delta$ = 3.25 (ddd, $J$ = 13.6, 7.6, 7.2 Hz, 2 H, 1-$H_2$), 2.35 (dd, $J$ = 9.2, 4.4 Hz, 1 H, 3-H or 4-H), 2.17 (dd, $J$ = 6.4, 4.4 Hz, 1 H, 3-H or 4-H), 2.04 (dddd, $J$ = 9.2, 7.6, 7.2, 6.4 Hz, 1 H, 2-H) ppm. $^{13}C$ NMR (100 MHz, $D_2O$): $\delta$ = 175.2 (C-5 or C-6), 173.8 (C-5 or C-6), 36.9 (C-1), 27.3 (C-3 or C-4), 26.9 (C-3 or C-4), 24.3 (C-2) ppm. HRMS (ESI): calcd. for $C_6H_{10}NO_4^+$ [M + H]$^+$ 160.0610; found 160.0609.

**(1*R*,2*S*,3*S*)-2-(Ammoniomethyl)-3-carboxycyclopropanecarboxylate (*meso*-3-*epi*-*N*-Desmethyldysibetaine CPa, 52):** A suspension of 3-*epi*-*N*-Boc-amino diester **50** (2.0 mg, 0.0063 mmol) in hydrochloric acid (6 M solution, 1.0 mL) was heated to 90 °C with stirring. After 24 h, the mixture was concentrated, and the residue was purified by column chromatography on reversed-phase silica gel (1 g, MeOH/$H_2O$, 10:90) to give 3-*epi*-DBCPa *N*-desmethyl analog **52** (1.0 mg, 100%) as a yellow solid; $R_f$ = 0.60 (BuOH/AcOH/$H_2O$, 33:33:33). IR (KBr): $\tilde{\nu}$ = 3446, 3225, 1634, 1456, 1399, 1353, 1267, 1038, 891, 799 $cm^{-1}$. $^1H$ NMR (400 MHz, $D_2O$): $\delta$ = 3.42 (d, $J$ = 8.0 Hz, 2 H, 1-$H_2$), 2.35 (d, $J$ = 8.8 Hz, 2 H, 3-H and 4-H), 1.85 (m, 1 H, 2-H) ppm. $^{13}C$ NMR (100 MHz, $D_2O$): $\delta$ = 173.7 (2×, C-5 and C-6), 35.4 (C-1), 25.0 (2×, C-3 and C-4), 19.9 (C-2) ppm. HRMS (ESI): calcd. for $C_6H_{10}NO_4^+$ [M + H]$^+$ 160.0610; found 160.0603.

**Supporting Information** (see footnote on the first page of this article): $^1H$ and $^{13}C$ NMR spectra of new compounds, NOESY spectrum of *cis*-cyclopropane **17**, as well as chromatographic comparison of synthetic DBCPa (**1**) with its natural counterpart.

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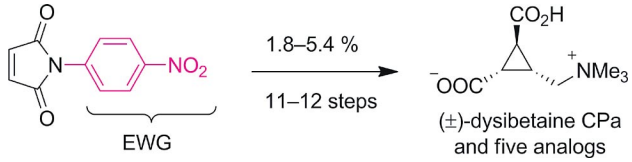
**Total Synthesis**




The syntheses of the marine sponge-derived γ-amino carboxylic acid dysibetaine CPa and five analogs in their racemic forms were successfully performed by taking advantage of an electron-withdrawing *N*-(4-nitrophenyl) group in the cyclopropanation reaction, the reductive ring opening of an imide, and the ethanolysis of an *N*-Boc-protected imide.

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Total Synthesis of (±)-Dysibetaine CPa and Analogs

**Keywords:** Total synthesis / Natural products / Amino acids / Neurological agents / Diastereoselectivity / Chemoselectivity

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